NO pills IN WATERS

Investing in Opportunities

This project has received European Regional Development Funding through INTERREG IV B.

INTERREG IVB

Interreg IV B NWE project partnership 2012 - 2015

noPILLS report

Summary

Pharmaceuticals in the Environment (PiE) are an increasingly recognised risk to the quality of surface water and groundwater.

The noPILLS project contributed towards a better understanding of the complex system of processes and – probably more importantly – actors that influence the presence of pharmaceutical micropollutants in waste water and, ultimately, receiving waters.

Clearly, a problem as complex and wide-ranging as that of pharmaceuticals in the aquatic environment cannot be comprehensively explored by a single project. However, noPILLS aimed to provide a unique insight into the problem by first defining the range of factors affecting pharmaceuticals in the environment, together with related points for intervention, and then investigating these interventions in a multi- and inter-disciplinary fashion. In developing the concept of a "medicinal product chain" (of processes and actors), noPILLS identified potential "levers for intervention" towards the reduction of pharmaceutical ingress into the aquatic environment.

This report describes a series of case studies of applied investigative nature along the medicinal product chain, which explored and evaluated a range of levers for intervention for their underlying efficacy, efficiency, barriers and challenges.

In summary, the noPILLS project has shown that:

- Pharmaceutical micropollutants are ubiquitous in the aquatic environment in the project areas, and contribute to environmental effects;
- Regional differences exist in environmental conditions, as can be expected due to macro-geographical influences (landscape, climate etc), but conditions can also vary within regions and in time, with the biggest factors being influx of effluents and dilution in the environment;
- A risk highlighted by noPILLS is that of antibiotic resistance developing in - or being introduced into - the aquatic environment via the sewerage network;
- People, acting both as consumers/patients and as professionals, play an important role in the medicinal product chain and need to be involved more in intervention activities;
- Strong regional differences exist in factors that are influenced by human behaviour, attitudes, and awareness; most likely this is primarily a result of regional differences in systems (e.g. health system, funding, waste management);
- There appears to be a relatively high level of underlying willingness to 'do the right thing' both by the general public and professionals, which is largely under-utilized due to lack of information, support or means to change behaviour;
- Technological interventions are effective in reducing some pharmaceutical micropollutants but present their own challenges in terms of monetary and energy costs;
- Training, education and awareness raising, together with good stakeholder management and effective communication, are crucial for the success of all forms of intervention.
- There appears to be no single 'silver bullet' intervention point, and the whole medicinal product chain needs to be considered for multi-point, targeted intervention.

Table of content

Tables and Figures

Figures

Tables

Text Boxes

List of abbreviations and acronyms

AMR = Antimicrobial Resistance

ARB = Antibiotic Resistant Bacteria

CAS = Conventional Activated Sludge

CHAL = Centre Hospitalier Alpes-Leman

CHEM = Centre Hospitalier Emile Mayrisch

CSO = Combined Sewer Overflow

D = Germany

EMA = European Medicine Agency

F = France

EG = Emschergenossenschaft

GSL = general sales list

GCU = Glasgow Caledonian University

GP = General Practitioner

HWWTP = Hospital Waste Water Treatment Plant

ICM = Iodinated X-ray contrast media

INN = international non-proprietary name

IT = Information Technology

LIST = Luxembourg Institute of Science and Technology

LOQ = Limit of Quantitation

Lu = Luxembourg

LV = Lippeverband

MBR = Membrane Bioreactor

NHS = National Health Service

NHSScotland = National Health Service Scotland

NL = The Netherlands

OTC = Over The Counter

PE = Population Equivalent

PEC = Protonic Exchange Capacity

PEC = Predicted Environmental Concentration

PIL = Patient Information Leaflet

PNEC = Predicted No Effect Concentration

PILLS = Pharmaceutical Input and Elimination from Local Sources (noPILLS precursor project)

POM = Prescription only medicines

RIVM = Dutch National Institute for Public Health and the Environment

RPS = reference pricing system

SES = socio-economic status

SIPIBEL = Site Pilote de Bellecombe

TF = Trickling Filters

UK = United Kingdom

UniLim = Université de Limoges

WHO = World Health Organisation

WWTP = Wastewater Treatment Plant

1. INTRODUCTION

1.1 Background and project aim

The noPILLS project is a partnership of 6 partners from 5 countries (D, F, LU, NL, UK) dealing with pharmaceutical residues in the environment with the focus on water. It started work in 2012 with EU funding from the Interreg IVb programme and presents its results in 2015.

The noPILLS project was developed taking into account results of the previous PILLS project which, from 2008-2012, dealt with the efficiency of – and requirement for – treatment technologies at pharmaceutical pollution point sources (mainly hospitals). Four of the six noPILLS partners cooperated in the PILLS (2012) project. They extended the project topic from the 20% of the human medicine residues in waste water originating from hospitals (dealt with in the PILLS project) to include the remaining 80%, which arise within a river catchment area and mainly originate from households but also decentralised care installations, industry and commerce.

Equally important, the PILLS project results indicated that engineering and technical solutions alone would not be sufficient to result in a comprehensive reduction of all potentially toxic pharmaceutical residues, especially not at acceptable monetary and energy / CO_2 cost. From this came the recognition that successful abatement measures will also have to address routes into the environment within the catchment (and not only end-of pipe) and involve society at large in reducing human pharmaceutical input into the environment.

Moreover, the EU activities focussing on preserving and improving the aquatic environment in Europe have led to the inclusion of three pharmaceuticals on a watch list in 2013 (Directive 2013/39/EU, 2013). In 2015 three additional macrolide antibiotics were added to the watch list (Commission Implementing decision (EU) 2015/495, 2015). The objective of the implementation of the European watch list is to update the available information on the fate of the listed substances in the aquatic environment and consequently, to support a more detailed environmental risk assessment.

In this context, the noPILLS project aimed to provide further information on the fate of pharmaceutical residues in the aquatic environment, and to provide, via a number of case study approaches throughout the project partnership, practical experience on the identification of potential and actually implemented technical and social intervention points across the medicinal product chain (see Chapter 2) with a focus on consumer behaviour, waste water treatment and multi-stakeholder engagement. The focus of noPILLS is on pharmaceuticals for human consumption; medicinal products for veterinary use have not been studied in detail, although they might form part of the observed pharmaceutical load in the environment.

From previous experiences of the noPILLS partners, a number of key research questions on pharmaceuticals in the environment were identified and sought to be addressed:

- To what level of detail is the "medicinal product chain" known in terms of stakeholders and actors? Considering the whole medicinal product chain – from development and production by the industry, authorization, marketing, legislation, physicians' choices and prescribing practices, pharmacies, health insurance, patients' choices and expectations, consumption pattern, disposal behaviour etc. – which factors influence the release and fate of pharmaceuticals in the environment and to what extent?
- Can emissions of pharmaceutical residues to the water cycle be reduced by segregation measures at source and subsequent separate disposal or treatment?
- To what extent does wrong disposal and incautious handling of pharmaceuticals contribute to the pharmaceutical load in waters?
- If the assumption is validated that a considerable portion of the load has its origin in consumption and behaviour pattern: is there a realistic chance to reduce the impact significantly by information, education and training?
- Can advanced treatment steps at municipal wastewater treatment plants – under realistic operating conditions – contribute to the reduction of pharmaceutical substances in the environment?

In order to span the wide range of research questions, the noPILLS partners worked in a multi-disciplinary project team, ranging from social science to engineering, biological sciences and IT, and actively sought exchange and collaboration not only between the various disciplines but also considered questions of consumption and disposal behaviour in the light of different cultural and administrative contexts.

In essence, the main aim of the noPILLS partnership was to contribute to the European discussions and decision-making process regarding the increasingly recognised problem of pharmaceuticals in the environment.

According to Directive 2013/39/EU "the Commission shall […until September 2015] develop a strategic approach to pollution of water by pharmaceutical substances. That strategic approach shall, where appropriate, include proposals enabling, to the extent necessary, the environmental impacts of medicines to be taken into account more effectively in the procedure for placing medicinal products on the market. In the framework of that strategic approach, the Commission shall, where appropriate, by 14 September 2017 propose measures to be taken at Union and/or Member State level, as appropriate, to address the possible environmental impacts of pharmaceutical substances […] with a view to reducing discharges, emissions and losses of such substances into the aquatic environment, taking into account public health needs and the cost-effectiveness of the measures proposed." The noPILLS project aimed to contribute to this process with the aforementioned multi-disciplinary and trans-regional approach towards gaining and sharing practical experiences from the actual implementation of potential 'levers for intervention' along the medicinal product chain.

1.2 The 'ethos' of noPILLS

The noPILLS partners formed a unique mix of organizations and staff from different backgrounds, providing complementary skills and opportunities to support investigative work:

- Emschergenossenschaft (EG) and Lippeverband (LV) are two German water boards that have long-term practical experiences in waste water treatment with nearly 60 treatment facilities ranging from a few thousand to several million people equivalents, in close cooperation with all the municipalities in the catchments with a total of 3.6 million citizens.
- The Université de Limoges (UniLim), associated with SIPIBEL (a site of experimentation and an observatory [www.graie.org/Sipibel/index.html]), and Glasgow Caledonian University (GCU) have scientists that work on highly topical research and provided a team of very different experts, bridging between disciplines of civil engineers, biologists, social scientists, communication experts and others.
- The Luxembourg Institute of Science and Technology (LIST) not only brought engineering expertise but also very close cooperation with many institutions and civil society within the Luxembourg community towards the project capabilities.
- The Dutch National Institute for Public Health and the Environment (RIVM) contributed a conceptual view of public health and environmental protection, and supported the partnership with a holistic meta-level analysis of the medicinal product chain and its processes and actors, thus providing overarching strategic input.

Overall, the noPILLS partners were convinced from the outset that there is no simple 'silver bullet' for the problem of pharmaceutical micro-pollutants, and that the problem can only be solved by interdisciplinary, long-term action focussed on establishing positive effects for society as a whole.

The project partners' intention for this report is to share their results and experience and thus contribute to the European discussion and subsequent decision making processes. The partnership is aware that the noPILLS project did not address all possible pharmaceuticals, processes, stakeholders or actors, but the noPILLS partners feel that their interdisciplinary case studies do address a significantly large and wide-ranging number of potential levers for intervention to provide a real contribution to the problem definition and solution.

1.3 noPILLS investigative activities and report structure

The noPILLS activities described in this report are broadly organised alongside the medicinal product chain (see Chapter 2), and demonstrate the extensive collaboration between disciplines and across regions. Given that one of the stated aims of the project partnership was to contribute to European discussions and decision making processes on the topic of abatement of pharmaceutical micro-pollutants, the partners wish to make specific reference and cognisance to the "BioIS study" (Bio Intelligence Services, 2013), and cross reference their noPILLS activities (Box 1) and recommendations (Chapter 8) to the BioIS study.

Following this introduction, the noPILLS report first describes the medicinal product chain and main actors in this chain; then provides results from the case studies on levers for intervention; and concludes with a summary of recommendations ("policy pointers") for intervention implementation:

- Chapter 2 develops the concept of the medicinal product chain from an actor (stakeholder) point of view.
  - The Dutch National Institute for Public Health and the Environment (RIVM) developed the medicinal product chain actor analysis, and conducted a literature search to explore user and stakeholder behaviours, knowledge and awareness, thus providing a theoretical framework for other partner activities.
- Chapter 3 describes monitoring activities of pharmaceutical micropollutants in sewage systems and receiving waters.
  - Emschergenossenschaft (EG), Lippeverband (LV), the Université de Limoges (UniLim), Glasgow Caledonian University (GCU) and the Luxembourg Institute of Science and Technology (LIST) monitored the presence of pharmaceutical micropollutants in sewers and receiving waters;
  - UniLim, association with SIPIBEL, and GCU monitored the ecotoxicological effect of micro-pollutants in water;
  - UniLim developed methods to quantify antibiotic resistance in water samples and applied these in the monitoring campaigns;
  - UniLim evaluated the impact of stabilization treatment on the fate of pharmaceutical compounds in sewage sludge.
- Chapter 4 considered reducing the pharmaceutical load at source: engaging society about pharmaceutical consumption and disposal. One of the significant conclusions to emerge from the previous PILLS study was that whilst there might be a number of technical solutions to the problems associated with pharmaceuticals in the environment, to obtain a greater understanding of the broader issues, any future study would need to engage directly with members of the general public, both as medicine consumers but also as consumers of water resources. For this reason, here we consider directly their understandings of medicine use (and associated storage and disposal issues) and also those related to environmental impacts.
  - GCU explored in a large qualitative programme of interviews with members of the general public their attitudes to medicines (consumption, storage and disposal) and behaviour change, and explored in workshops realistic solutions and notions on (environmental) responsibility and achieving behaviour change;
  - UniLim undertook a similar, albeit more quantitative, study involving members of the general public on consumption, storage and disposal, and towards realistic solutions;
  - LV conducted a large case study in the local town of Dülmen, focusing both on capturing attitudes and behaviours, and on implementing and evaluating intervention in the form of awareness campaigns. This included public awareness campaigns over one and a half years and involved not only members of the public but also medical and pharmaceutical professionals and various other stakeholders.
- Chapter 5 concerns reducing emissions of pharmaceutical residues to surface waters by implementing measures of source segregation.
  - LIST and EG conducted measurement campaigns at hospitals to evaluate the effectiveness of urine bags as a means for source segregation at hospital level;
  - LIST and EG also supplemented the chemical measurements with an evaluation of patient and hospital staff feedback on the measurement campaigns.
- Chapter 6 discusses removal of pharmaceuticals by advanced treatment of (hospital) wastewater.
  - EG conducted a long-term case study on the performance of a full-scale hospital wastewater treatment plant using ozonation and powder activated carbon;
  - LIST evaluated the removal of pharmaceutical residues in a biologically pre-treated wastewater using biological activated carbon;
  - UniLim with SIPIBEL/Suez compared decentralised and centralised treatment options for hospital effluents using various biological process configurations, membrane filtration, ozonation and activated carbon;
  - GCU and EG investigated removal of pharmaceuticals from wastewater by advanced oxidation using ferrate.
- Chapter 7 evaluates tools for targeted communication campaigns.

- LV evaluated tools for community-wide communication campaigns in the 'case study Dülmen', directed at various target groups: community-wide, medical and pharmaceutical professionals, general practitioners and their patients, pharmacists and their customers;
- GCU explored modern media and processes as communication tools: 3D virtual reality systems for information dissemination, and "Game Jams" as both a means to engage media professionals and create 'serious games' as a tool for awareness creation and learning.

- Chapter 8 provides summaries of all activities, conclusions and suggestions for intervention levers that could be considered by policy makers and wider stakeholders for adoption or further investigation. noPILLS "policy pointers" are cross-referenced to BioIS "factors of influence".

The noPILLS partnership, as outlined above, provided a unique mix of disciplines and organisational capabilities for the practical and theoretical exploration of several of the identified levers for intervention along the medicinal chain. This resulted in a mix of trans-disciplinary investigations ranging from the exploration of attitudes to medicines in the general public, via exploration of actual behaviour change, to engineering applications and the development of communication campaigns and tools.

In parallel (but not connected) to the noPILLS project, a preparatory "study on the environmental risks of medicinal products" was commissioned by the Executive Agency for Health and Consumers and published on 12 December 2013. This "BIO IS study" discusses a wide range of legislative and non-legislative "factors of influence" and related possible solutions.

There is considerable congruence between the BioIS non-legislative factors of influence and possible solutions, and the noPILLS 'levers for intervention' along the 'medicinal product chain'.

Whilst the noPILLS project and the BioIS study were completed independent of each other, it is clear that both came to very similar conclusions as regards possible intervention measures, and the noPILLS partnership feels that the high congruence between these two independent research activities lends additional weight to the results drawn in either study.

With the BioIS study clearly having a much broader remit - including legislative factors of influence – it is also clear that the noPILLS study provides added value to the BioIS study in the form of practical experiences on the implementation of the theoretical considerations described in the BioIS study.

In order to make explicit the complementarity and added value presented in this overlap, this box cross-references the noPILLS activities against the nine non-legislative possible solutions identified in the BioIS report.

The noPILLS project provides further insight, gleaned from practical implementation, on seven of the nine BioIS strategic groups of non-legislative solutions:

1. Developing the concept of green pharmacy and adapting packaging to influence consumption;

2. Developing and harmonising the implementation of collection schemes for unused medicinal products; (noPILLS report Chapter 4)

3. Developing source separation measures; (noPILLS report Chapter 5) **and wastewater treatments**; (noPILLS report Chapter 6);

4. Actively involving public society and professionals through information and education; (noPILLS report Chapter 2, Chapter 3 and Chapter 7);

5. Prioritising and monitoring molecules and/or environmental compartments of concern; (noPILLS report Chapter 3, as well as the whole previous PILLS report)

6. Consolidating existing knowledge, ensuring transparency and facilitating access to information; (noPILLS project overall as a knowledge exchange activity)

7. Improving governance and building up an eco-pharmacovigilance network;

8. Implementing incentive economic instruments; (noPills report Chapter 2, analysis of the medicinal product chain on the roles of insurers and the decision process concerning reimbursement)

9. Developing the knowledge base through fostering of research activities; (noPILLS project overall as a joint research project with a focus on multi-disciplinary work).

Box 1.1: Complementarity and added value between noPILLS activities and BioIS study

2. Formulating understanding of actors and processes: identification of levers for intervention

2.1 The medicinal product chain

This chapter presents the medicinal product chain from design of pharmaceuticals through to production, licensing, prescribing, dispensing, use, disposal, and ingress and fate of medicinal product residues in the environment. Taking into account the entire medicinal product chain, many actors and processes can be identified that play a role and that could possibly influence the flow of medicinal product residues into the environment, where they pose risks for organisms living there.

The decision to map the process prior to medicinal product influx into the wastewater system is founded in the observation made in all European countries that monitor the chemical quality of their water bodies: the presence of medicinal product residues (see also BIO Intelligence Service, 2013), together with the expected increase in use of medicinal products. One way to handle this is to improve wastewater treatment in order to avoid discharge of such compounds into the environment. However, this end-of-pipe approach will require high investment and running costs, and may not solve all the problems (PILLS, 2012). Another, more integrated and, arguably inherently more successful, approach is to look also for possibilities to reduce ingress of such medicinal product residues into wastewater and, subsequently, surface waters, groundwater and other environmental compartments. Therefore, mapping of the whole medicinal product chain was undertaken by RIVM in the noPILLS project. This chapter summarises an extended study to be published in an RIVM report (in prep.), and thus does not pretend to be exhaustive.

In the medicinal product chain, relevant actors and processes were described, and potential levers for change were identified where stakeholders may have the opportunity to adapt their activities, which may ultimately result in lower discharges of medicinal product residues into the environment. The focus of this work was only to identify potential levers for change; further research is necessary in order to make an integral assessment of the feasibility of intervening on these levers and the effects these interventions may have. However, noPILLS project investigative activities have already focused on several of these levers (see Chapters 3-7), and the partnership suggests that these results may be considered by policy makers and other actors in the choice of intervention measures (Chapter 8). Clearly, no single research activity, such as the noPILLS project, will be able to address all aspects, processes and important actors in the medicinal product chain and we suggest that, in subsequent investigations, the effects and feasibility of intervention at the various specific levers be further investigated to provide information on how this could best be achieved.

The mapping of the chain in this study was confined to medicinal products for human consumption; pharmaceuticals for veterinary use have not been studied in detail, although they might cause part of the observed pharmaceutical load in the environment. The RIVM medicinal product chain description was primarily based on the Dutch situation (RIVM report in prep).

In a preliminary comparison study between the situations of UK (Scotland), Germany (North Rhine Westphalia) and the Netherlands, using specifically prepared lists of questions and discussions with national experts, we identified important differences between these countries and regions. Where relevant, international comparisons are made in this chapter, which highlight the need for regionalisation of some levers for intervention.

A summary of the different phases in the medicinal product chain, including a selection of the most important actors and processes is given below, as well as examples of potential levers for intervention. Furthermore, transnational differences in the structure of the medicinal product chain are pointed out.

Figure 2.1: Simplified medicinal product chain, showing processes and actors at each phase, based on the Dutch situation, but applicable in a conceptual way to several other western countries. The numbers in the figure correspond to the phases described in this chapter. An interactive version with more detail and drill-down functionality is available at http://www.rivm.nl/en/Topics/P/Pharmaceuticals_in_the_environment and via www.no-pills.eu.

Phase 1. Development of new medicinal products

The most important actor in the development of new medicinal products is the pharmaceutical industry.

In this process, the pharmaceutical industry is influenced by, for example, market demand, financial considerations and legislation.

Development and production of new drugs is performed by multinational companies, that sell their products in different countries. No major differences in this stage of the medicinal product chain were observed between the different countries.

Phase 2. Registration and market access

Important actors in this phase of the medicinal product chain are the European Medicine Agency (EMA) and national Medicine Agencies for the assurance of the quality of medicinal products and for the marketing authorization. Furthermore, national Medicine Agencies decide on the legal status of supply of the medicinal product (i.e. whether it needs to be prescribed by a physician or is available over-the-counter (OTC)). In the Netherlands, after marketing authorization is granted and legal status is decided upon, the Dutch National Health Care Institute (Zorginstituut Nederland) advises on whether or not the medicinal product will be reimbursed by the Dutch health care insurers.

Potential levers for intervention may be found in the registration process (for example, introducing environmental consequences into the review process for registration and marketing authorization) and in the decision process on reimbursement and legal status of supply (for example by making persistent pharmaceuticals less easily available).

The registration of new medicines is a process where nationally and internationally operating regulating and registration bodies play their roles: the international comparison revealed that national registration authorities of different countries make different decisions, for instance on the categories of OTC medicinal products and the places where they can be sold. This will cause differences in access to medicines (OTC medicines are more easily accessible) across countries, and could be a cause of different consumption patterns.

Phase 3. Production and distribution of medicinal products

Important actors in the production and distribution process are the producers of pharmaceutical products (both international and national), pharmaceutical wholesalers, importers and providers of pharmaceuticals (i.e. the pharmacy, the drugstore). Good manufacturing practices and good distribution practices are important guidelines and strict monitoring of their compliance is important. Potential levers for intervention may be the inclusion of environmental aspects in these guidelines, as is the case already in the Industrial Emission Directive, and so-called green pricing.

Phase 4. Consumption of medicinal products

(either on prescription or as self-medication)

Important actors in this phase of the medicinal product chain are the patient, the physician (general practitioner (GP) or specialist in hospital), the insurer, the pharmacy and the drugstore. Many factors influence the process in which medicinal products are prescribed and delivered to patients, either by the GP or in the hospital. Doctors are influenced by guidelines, their experience and their active medicine arsenal, but also by patients' communication and expectations. Environmental awareness among doctors and patients and introduction of environmental aspects into guidelines might be potential levers for intervention to influence consumption patterns. Furthermore, e.g. in cases of chronic or preventive drug use (e.g. statin use to control cholesterol), changes in lifestyle or diet could be taken into consideration, to avoid or decrease medicine use. Insurers may influence availability of medicines by selecting preferred medicines for reimbursement; environmental criteria could be introduced into this process. Insurers, doctors and pharmacies might increase their endeavours to deliver medicines in appropriate amounts. Pharmacies and drug stores provide user-information with regard to the medicines that are delivered to the patient; environmental aspects could be part of this information exchange. It becomes clear that the quality of the relation between patient and professional affects the acceptance of advice by the patients (see also Chapter 4 and 5). Having trust in the doctor is said to affect how likely it is that the doctor's advice is accepted. Besides information from professionals, informal sources of information affect patients' consumption choices: family and friends, the Internet and personal experience are taken into account when deciding to use medicinal products.

The international comparison revealed that the reimbursement of medicines and the payment of physicians are organized differently in different countries. This also seems to influence doctors' prescribing behaviour. Furthermore, the organization of the health care system differs in certain aspects; whereas in the Netherlands and Scotland the GP is either a family doctor who knows the patient's medical history or he works in a local practice and has access to the medical history via practice records, in Germany a patient has the possibility to 'shop around' for a physician and the GP does not necessarily have an overview of the total medical status of the patient. In France, the patient has a referent physician. Patients who consult other physicians get only limited reimbursement. The different role of the community pharmacist in the different countries (ranging from close to no cooperation between the pharmacists and GP in the UK; the pharmacists as an advisor of the physician in Germany; and a relatively close cooperation between the pharmacist and the GP in the Netherlands) is another example of the differences between the health care systems. (See also Box 2.1)

Phase 5. Disposal of medicinal products

Important actors in this phase of the medicinal product chain are the patient, the pharmacy, the municipality and the hospital. Medicine use

UK – Prescription only medicines (POM) are made available principally to the public by a medical practitioner, although historically dentists have been able to supply from a limited Dental Formulary (mainly antibiotics or analgesics). GPs, hospital consultants and dentists are referred to as independent prescribers. In the UK there are a second set of prescribers "supplementary prescribers", who are able to write prescriptions in accordance to specified clinical management plans. These plans are agreed between the supplementary prescriber, the doctor and the patient. Certain nurses can become supplementary prescribers provided that they complete additional training. Other groups of health professionals have a limited supply of certain drugs in the UK – these included paramedics who can administer certain named drugs under their own initiative in emergency situations and this legislation is under regular review. Chiropodist and podiatrists may also administer certain prescription only medicines in the course of their practice; this is heavily regulated (The Human Medicines Regulations, 2012). Much of the change in the prescribing practices in the UK has taken place with a change in the categorisation of many drugs. The flow is POM to P (Pharmacy only) to GSL (general sales list). POM medicines must be prescribed by an independent prescriber, P medicines can be bought (and in some cases be supplied free of charge) from a pharmacy and a pharmacist must supervise the sale, and GSL medicines can be sold through general retail outlets provided they are pre-packed. Often, the strength and pack size of GSL medicines are limited and higher strength formulations or larger packs have a P or POM license; this is different from the prescribing legislation detailed above and relates to the category of medicine on the "general sales list" (GSL), which is least controlled. Overall, there appears to be a move towards self-medicating and supplementary prescribers.

Germany – Prescribing remains with medical practitioners and there is little evidence of devolvement of this practice being considered in the literature. In Germany, pricing of medicines is officially unregulated even though the authorities influence medicine prices through the reference pricing system (RPS) (Vogler and Schmickl, 2010). Physicians are not required to prescribe by international non-proprietary name (INN). However, physicians' budgets and computer prescribing systems encourage generics prescribing. If the physician issues a prescription for a specific medicine without excluding substitution, the pharmacist must dispense the prescribed medicine or one of the three cheapest alternatives. However, pharmacists have no incentive to dispense generics and are in fact financially penalised when doing so due to fixed margins. Patients' co-payments should encourage demand for generic medicines, and the government has attempted to inform patients of generic medicines.

The Netherlands – In The Netherlands, doctors, dentists and midwives are qualified to prescribe medicines. Since 2012, nurse specialists and physician assistants have been allowed to prescribe medicines as well, though constrained to the less complex types of medication. Nurses working in specific areas such as diabetes care may prescribe medicines, but also under certain conditions. Prescribed medicines, dispensed to out-patients, are provided by independent pharmacies and dispensing GP's (KNMG, 2015). A free-pricing system has been in place since 2012, which means that health insurers negotiate with pharmacies and dispensing GPs about the prices of pharmaceuticals and services. Since 2008, health insurers have also been allowed to identify a preferred medicine within a group of medicines and fully reimburse the preferred medicine only. In this way, they have been able to stimulate a more efficient use of medicines (NZA, 2014, WHO, 2010). Besides, national regulations have influenced the pricing of medicines. Most importantly, a reference pricing system exists, which dictates that prices cannot exceed the average price level in Belgium, France, Germany and the UK (Drug Price Act, 'Wet Geneesmiddelenprijzen'WGP; WHO, 2010; Zorginstituut, 2014). Medicines dispensed to in-patients are included in the inpatient (hospital) payment system, which is similar to Diagnose Related Group-like (DGR) products reimbursement. Here again, health insurers and hospitals negotiate about the price and volume of pharmaceutical products. Health insurers stimulate pharmacists to carry out generic substitution, without need for reference to the physician (WHO, 2010). Patients may need to pay a higher co-payment, out-of-pocket, or use the mandatory deductible in case they want to use a non-preferred medicine. Therefore, they have a clear incentive to use specific medicines.

France – In France, prescribed medicines are obtained via prescriptions from medical practitioners although there is a great availability of medications in pharmacies and there is some prescribing ability of the pharmacists in France for certain medicines. As France moves to liberalise access to pharmaceuticals by the general public, there are more over the counter medicines in France and since 2008 pharmacists have been permitted to sell some medicines without prescriptions. Since 2013 non-prescription medicines are available in super markets. In 2015, there are over 500 medicines available for sale this way and the market is worth over €2 billion per year. The level of transparency over the prices of over the counter medicines is often rather poor. Some medicines will be shown openly on the shelves of the chemist 'en libre service', whilst certain others will only be available 'derrière le comptoir', requiring that you ask the chemist for them. Not only are the prices for behind the counter medicines rarely visible, but numerous consumer surveys have shown that those medicines are often cheaper alternatives to those on the front shelves. One of the main reasons is that some of these medicines are price controlled by the government, as they are also available on prescription.

Luxembourg – Luxembourg appears to be more liberal in the prescribing range than France, Germany or The Netherlands. Limited information is available in the literature but like Germany, The Netherlands and France, it is doctors only who are able to prescribe medicines. Doctors cannot provide a prescription to a pharmacist over the phone, however pharmacists may modify scripts by calling the doctor. Prescriptions are reimbursed in Luxemburg by the state and in Luxembourg pharmacists have a greater responsibility for the patient's health and safety than the doctor. This is because the pharmacist is held responsible for selling medicines or remedies if they lead to further illness or result in adverse side effects, even if the medicines were prescribed by the physician. (Expatica, 2012).

Box 2.1: Comparison of access to medication through prescription and purchasing. Note: this review (by GCU) does not claim to be comprehensive or reflective of all current practices; it aims to demonstrate differences as would be evident to trans-national decision makers from consultation of literature alone.

by patients may result in excess or out of date medicines. The behaviour pattern with regard to medicine use and disposal might be influenced by increasing the environmental awareness of the patient.

The noPILLS project provides much research evidence in this respect (see Chapter 4 and 5). Scottish results show that safety is a more prominent reason to dispose of medicines than environmental consequences. Consequently, medicines are disposed of both 'properly' by returning them to a pharmacy and 'improperly' through the toilet. Disposal of unused medicines through proper channels (i.e. ideally returning them to pharmacies where possible or via the solid waste stream) could be increased by facilitating this process. The results from Scotland and Germany show that people say they are willing to dispose of medicinal products in a more environmentally sensitive manner once they are aware of potential problems. Experiments with providing patients with urine bags in order to prevent medicinal product residues from entering wastewater also point to this type of source separation as a potential lever for intervention (see Chapter 5). In France, the Cyclamed association, approved by the French Government, is to collect and value the unused medicines (MNU) for human use, expired or not, reported by patients at pharmacies (http://www.cyclamed.org). The estimated recovery rate in 2014 was 63% of unused medicinal with a collected tonnage of 12,056 tons, and an increase of + 1.7% compared to 2013.

Phase 6. Treatment of municipal waste containing medicinal residues

The actors important in this phase are mainly the managers of the wastewater treatment plants and solid waste treatment companies, as well as the competent authorities responsible for the collection of waste streams (e.g. municipalities and water boards but also national governments). There are three important routes of medicinal product residues: after ingestion through the patient via the toilet into the sewer system, direct disposal into the sewer system and disposal into solid waste (either in municipal waste, in waste collected as minor chemical waste or medicinal waste collected at the pharmacy).

Medicinal product residues in the sewer system are partly removed in a municipal wastewater treatment plant, under the responsibility of a water board or municipality. After this step, the wastewater is discharged into surface waters. When there is no wastewater treatment plant, wastewater might be cleaned locally in a septic tank. In some rural areas, houses are not connected to sewer systems and municipal wastewater plants and the waste water is discharged directly to the surface water or into the soil. Wastewater of hospitals or pharmaceutical companies may be treated directly on site, before delivery into the sewer system. Part of the medicinal product residues are not removed in a wastewater treatment plant, and are discharged with the effluent into the surface water. The excess sludge of the wastewater treatment plant may be incinerated, disposed of in landfill sites, or spread onto agricultural land. Medicinal waste that is discharged as solid waste may be incinerated in waste incineration plants, or disposed of in landfill sites.

Potential levers for intervention are for example: improvement of purification techniques (see e.g. Chapter 6), the development of techniques to separate and treat waste at the source (e.g. special toilets and urine bags), and placing wastewater treatment plants at hospital sites (see e.g. case study in France/Germany/Luxembourg in Chapter 6).

Several differences between countries were revealed in the international comparison. In The Netherlands and Germany (North Rhine - Westphalia), the majority of wastewater is treated in municipal wastewater treatment plants, and most sewage sludge is incinerated; whereas in Scotland's rural regions, there is strong reliance on private micro-treatment plants and soil infiltration, and about 50% of the wastewater sludges are recovered for recycling to agricultural land. In many of the other German Bundesländer, sewage sludge is also applied on agricultural lands, as is true in France, where 639 000 tons of dry matter are spread on farmland as organic amendment (2010), or about 60% of the urban sludge produced in the country. Similarly, most solid waste is incinerated in North Rhine-Westphalia and the Netherlands; however, in Scotland most of the solid waste is landfilled, with the risk of leachate escaping in groundwater and surface water. This difference in organization of waste treatment also suggests a different approach to informing the public on how to dispose of excess and out-of-date medicinal products. In Germany most solid waste is incinerated (North Rhine Westphalia) and medicine recollection schemes there were discontinued.

Phase 7. Fate of medicinal residues in environment and human resources

Although there are no direct actors involved in the processes in this phase, researchers play a role in building up a knowledge base, which may be used higher up in the chain, for example in the development phase.

Once a medicinal product ends up in the environment it may be partly degraded or adsorbed to soil and sediment particles. These residues will not give environmental problems while they are not bioavailable, however bioavailability may change with altering environmental conditions. The bioavailable part will be taken up by organisms and may affect their behaviour, characteristics, or survival. Once medicinal products have entered the environment, their behaviour cannot be influenced. Research on

fate and effects of such compounds may help to prioritize the development of measures to prevent introduction of specific compounds into the environment.

The discharge of antibiotics into the environment, for example, can lead to adaptation of microorganisms that then become resistant (see French case study in Chapter 3); an aspect requiring further research. Spreading of resistance genes into the environment, either through discharge of effluents of waste water treatment plants or through discharge of sewage sludge onto agricultural land, may lead to reduced effectiveness of antibiotics in the control of infectious diseases in humans and animals. Some medicinal residues will enter water bodies used in agriculture for irrigation of land or watering animals. This may lead to medicinal products in the food chain. Finally, yet importantly, residues could enter water bodies used as a source for drinking water. Conventional purification techniques for drinking water, like UV, activated carbon, ozone, chlorine, sand filtration etc., do not remove all medicinal waste products in the water. And in some locations (e.g. Scotland's remote regions) private water supplies may employ none or only very basic purification techniques.

2.2 Detailed actor analysis

RIVM conducted a literature search, utilising prior patient surveys, public policy documents, stakeholder publications, and peer reviewed literature to explore prescribing behaviours, consumption behaviours, knowledge and information (sources), storage and disposal patterns, and awareness of environmental issues in the Netherlands. This review was restricted to Phases 4-6 of the medicinal chain in order to concentrate on evaluation of potential levers for intervention where prior experience existed within the wider noPILLS team.

2.2.1 Introduction

According to the OECD (2014) medicine use is increasing. When a patient has a health problem and decides to take action, they can decide to self-medicate or to go to a doctor, where they might receive a medicine prescription. When patients decide to seek professional help, they expect the doctor to be able to solve their health problem. Many health problems are dealt with by means of prescribing medication. However, some health problems, especially chronic conditions such as type II diabetes, high-blood pressure and high cholesterol, may be managed by lifestyle changes as well (Dickinson et al. 2006; Gillies et al. 2007; Mannu et al. 2013; Ornish et al. 1990). In these cases, medicine prescription may be reduced.

2.2.2 Prescribing and dispensing

Prescription of medicines is a complex process, in which the prescriber (e.g. GP, hospital specialist), the patient and the insurer are the main actors. Prescribing behaviour of doctors is subject to many influences:

Patient's presentation of problems

Primarily, medication prescription is determined by the problems presented to them by the patient. However, similar problems and diseases do not always lead to similar medical decisions (Denig and Haaijer-Ruskamp, 2005). Prescription guidelines exist for many conditions, but adherence to these is not always optimal, for example in the case of cardiovascular risk management and depression (Van Den Berg et al., 2014).

Practice- and patient-related factors

Practice- and patient related factors can greatly influence prescribing. In the Netherlands it was found that doctors with more high socio-economic status (SES) patients in their practice tend to prescribe a preference medicine (e.g. a branded medicine) more often than doctors with more low-SES patients(Lambooij et al., 2014). Doctors who have many elderly patients tend to prescribe more medication to their patients, even after controlling for age (Lambooij et al., 2014). Doctors tend to prescribe more medication to low-SES patients and in case of mental illness and urinary tract infections, female patients also tend to receive more medication prescriptions than male patients (Lambooij et al. 2014; Denig and Haaijer-Ruskamp, 2005).

Doctor-patient relationship

International research suggests that patients' expectations are an influencing factor in the doctor's decision to prescribe medication (Webb and Lloyd 1994). Perceived patient pressure is a predictor of doctor behaviour (Little et al. 2004), as it is important to doctors to maintain the therapeutic value of a good doctor-patient relationship (Butler et al. 1998). However, it has been suggested that doctors misconstrue these patient expectations and actually overestimate them (Lado et al. 2008).

Doctor-related factors

Evidence suggests that female GPs tend to be more patient-centred instead of task-oriented, which leads to lower prescription rates. Age and working experience do not necessarily influence prescription volume, but they do influence choice of medicines. The choice of medicine is also influenced by the doctor's active arsenal of medicines they have experience with, largely determined by their education. In the course of time, this arsenal is adapted under the influence of factors such as marketing by pharmaceutical companies, continuing education, consultation with colleagues and pharmacies and professional literature (Denig and Haaijer-Ruskamp, 2005).

Policy pointers:

- Prescribing is influenced by many factors other than therapeutic need. Marketing, guidelines, continuing education and professional literature may be useful media to influence prescribing behaviour to drive optimal therapeutic and environmental outcomes.
- Further research may be of value on the major influences on prescribing patterns – for example to inform further discussion on policy intervention points.

Insurer influence

The choice of medicines can also be restricted under the influence of the insurer. In the Netherlands, (the cost of) medicines are only reimbursed by the insurer when they are included in the Medical Reimbursement System. A reimbursement limit is established for each group of equivalent medicines (medicines with comparable clinical impacts). If a patient uses a more expensive medicine from the same group, he has to pay the excess himself unless the use of the more expensive medicines has a clinical justification, in which case this needs to be indicated on the doctor's prescription (Schafer et al. 2010). Furthermore, in certain cases insurers are allowed to use a preference policy, which means that for a group of equivalent (generic) medicines, they can choose to reimburse only one brand (usually the cheapest), unless it is clinically justified relevant. (Sanofi 2014; Zorgverzekeraars Nederland 2014)

Policy pointer:

- Insurers could be involved in discussion about reimbursement of environmentally friendly alternatives such as non-medicine treatments or 'greener' medicines particularly if governmental policy revealed a changing approach.

2.2.3 Consumption behaviour

Prescribed medication

After receiving prescribed medication, medicine adherence is largely the responsibility of the patient. Research shows that some patient groups find it more difficult to adhere to therapy than others. For instance, medicine adherence is often worse among older people compared to younger people. Type of symptoms and type of medication also influence adherence, as well as how many times a day medication should be taken (Paes and Smit, 2005).

Over-the-counter consumption

When individuals take medication without a doctor's prescription, they self-medicate. They buy a specific medicine for a specific symptom from a pharmacy, chemist or retailer or via the internet. The regulations as to where OTC medication can be sold and on which conditions, can vary across countries. In the Netherlands, chemists selling self-medication products are required to have a qualified 'druggist' (in Dutch chemist stores, only staff with a specific diploma are allowed to advise on medicines) present at all times when selling this kind of medication. They have a responsibility to only sell self-medication products to individuals and they need to ask every buyer if they need information or advice regarding the self-medication product (the so-called checkout-check) (PCO Certifying Body, 2015).

The possibility of self-medication is generally seen as beneficial, but has some drawbacks as well. Proponents of self-medication consist mainly of the government, pharmaceutical industry and patient organisations, as they argue that self-medication increases individuals' responsibility for their own health. Furthermore, it is cheaper than prescription medicine and it does not consume the doctors' time. However, opponents from medical practice argue that due to self-medication, some patients with more serious symptoms fail to go to the doctor in time, or even at all. Furthermore, medication monitoring is more difficult (Paes and Smit, 2005).

The influence of advertising

Another point of consideration is the balance between unlimited access to self-medication and patients' susceptibility to advertisements, which are often ambiguous in their claims (Paes and Smit, 2005). When buying self-medication, the consumer buys a medicine based on own experiences (or that of others) and influences, including advertisement.

Policy pointers:

- Advertising influences patient's decision to medicate and choice of medicine, and as such can (ultimately) have an environmental effect.
- Pharmacists can inform consumer on environmental consequences and proper way of disposal.

Over-the-counter medication

According to research in the United States, it appears that there are concerns with the use of self-medication products. Evidence suggests that despite wide usage, many people do not have enough information on when and how to take these products and may not consider important label information when buying self-medication products (NCPIE, 2002). Furthermore, label information is often not sufficiently understandable to the general public (Trivedi and Hannan, 2014). As a result of insufficient knowledge, there is a worry that consumers may take too much of a self-medication product or mix products inappropriately.

Policy pointer:

- Treatment outcomes from OTC use are not always optimal and, therefore, environmental gains may be achievable without adverse effects on treatment outcomes.

2.2.4 Sources of information

Prescribed medication

When a medicine is delivered to a patient, an exchange of information takes place. Furthermore, patients are increasingly able to communicate directly with their pharmacies to obtain information, and in some cases to order repeat prescriptions. This can in turn increase the accessibility of the pharmacy to some patient groups (Buurma et al, 2005). In case of first-time use, pharmacies are required to provide specific information with regard to the use of the medicine and the cost of this is reimbursed by the insurer. However, there is considerable evidence that many pharmacies have been failing to provide this service to first-time users of particular prescriptions (Mul 2014; NPCF 2014).

In hospital pharmacies, the process between receiving a prescription and delivering it to the patient is more complex both in terms of the number of professionals involved (e.g. doctors, nurses) but also sometimes in the actual preparation on site of medication. Furthermore, hospital pharmacies often do not deliver directly to patients; this mostly happens through nurses and doctors.

Policy pointer:

- If the ultimate aim is the reduction of pharmaceutical residues in the environment, including environmental consequences and appropriate disposal practices in information exchange when prescribing/delivering medicines might be useful.

2.2.5 Storage and disposal of medication by patients

One third of patients in the Netherlands who use medicines, sometimes have unused medicines in their household, which can result in medicine waste. In the UK, it is estimated that community care medicine wastage is in the order of 300 million pound per year (YHEC/School of Pharmacy, 2010). Reasons can include death of the patient; change in prescription; too large package sizes; repeat filling of prescriptions without assessing the amount at hand; not seeing the need for continuing medication following a therapy change by the doctor or the patients' subjective perception of an improvement of their condition (Reitsma et al. 2013; Vogler et al. 2014).

Policy pointer:

- Appropriate pack sizes may reduce medicine wastage. Issue of repeat prescriptions, change of therapy and death of patient (with due consideration!) may be appropriate moments to reinforce a correct disposal message or offer a collection service.

In the Netherlands, it was estimated that 2.9% of the medicines was returned to the pharmacy or chemical waste annually. Other types of disposal were not included in that study (DGV, 2006).

Patients dispose of their unused medicines in several ways. According to a survey in the Netherlands, about half of all patients return their

unused medicines to the pharmacy or the municipality's hazardous waste department; one in 10 people throw unused medicines in the bin and 2% reported to have disposed of their medicine in the sewer (toilet/sink) (Reitsma et al. 2013). A thesis on handling medicinal waste in relation to the Health Belief Model found that more than half of the respondents estimated their intention to return medicinal waste to the pharmacy as high (Berezowska, 2009)

Policy pointer:

- Disposal via toilet or sink still accounts for a considerable amount of pharmaceuticals; a worthwhile reduction could still be achieved by addressing this behaviour.

2.2.6 Awareness of environmental effects

60% of respondents knew that medicinal residues are found in the environment and that this may cause harm to themselves and the environment. This knowledge however was only moderately correlated to the intention to return medicinal waste to the pharmacy (Berezowska, 2009).

An international paper on disposal practices for unused medications that are around the world found that the type of medication may influence the manner of disposal. It is likely that people return unused medications considered to be harmful, to pharmacies (Tong et al. 2011). Furthermore, the environmental awareness of patients may also influence their disposal practices; several studies found that patients who returned unused medicines to the pharmacy did so out of concern for the environment. On the other hand, patients who disposed of their unused medicines primarily through the garbage or the sewage system did so out of convenience (Tong et al. 2011).

2.2.7 Summary

Purchasing choices by or for a patient are influenced by a chain of actors that are mutually interdependent and influence the processes of medicine use and disposal. First, the pharmaceutical industry and market access regulation authorities affect which medicinal products are available to choose from. Additionally, the distribution channel (OTC or prescription) affects availability and subsequent purchase and disposal of medicines. Next to the health issue that the patients have, physicians are known to make different choices in similar clinical situations. Also the reimbursement policy of the insurer affects which medicinal product is used. Changes by one or more of these actors, will affect whether the medicine needs to be disposed of. Patients have shown to be willing to conduct more effort to dispose of medicine in an environmental friendly way, if they are made aware of the problem, but this analysis also shows that also on the institutional level choices can be made to reduce the influx of potentially harmful compounds in the environment.

This review, whilst concentrating on the situation in the Netherlands, provides important generic policy pointers for consideration outwith their geographical context, and informed the engagement case studies conducted in the noPILLS project.

3 Pharmaceuticals in sewage systems and surface waters – status quo

3.1 Introduction

3.1.1 Background

This Chapter summarises new findings and insights relating to the occurrence of pharmaceuticals in the environment. With the introduction of the 'Watch List', which now features several pharmaceuticals (Table 3.1), a quantitative understanding of sources, available dilution and resulting concentrations of pharmaceuticals occurring in the aquatic environment remains important. Surface water measurement campaigns in the partner countries provide a useful 'snapshot' of levels of pharmaceuticals found in environmental waters, whereas waste water treatment plant (WWTP) influent and effluent concentrations, especially in combination with flow data, offer insights into the load discharged into the environment and dilution required to keep environmental concentrations below target levels, should these be set in the future. Sewage sludge is in some countries spread on agricultural land in the interest of nutrient cycling. Effects of pharmaceuticals on grazing animals have been established by Bellingham et al. (2012). Section 3.2 reports on concentrations and loads encountered in the course of our sampling campaigns in WWTP, rivers and sludges, including on the effect of stabilisation treatments on concentrations and partitioning of pharmaceuticals in sludge.

Name of substance/group of substances	CAS number(1)
17-Alpha-ethinylestradiol (EE2)	57-63-6 200-342-2
17-Beta-estradiol (E2), estrone (E1)	50-28-2, 53-16-7
Diclofenac	15307-86-5
Macrolide antibiotics: erythromycin, clarithromycin, azithromycin	114-07-8, 81103-11-9, 83905-01-5

Table 3.1: Pharmaceuticals on the 'Watch List', adapted from EC (2015)

Whilst the introduction of environmental quality standards for single substances, such as via the Directive on Environmental Quality Standards (Directive 2008/105/EC), offers some protection for environment, it does not fully account for the complexity of ecosystems and toxicity effects. Whole sample toxicity testing is complementary to pharmaceutical analysis; it can flag up mixture effects such as concentration additivity and take into account toxicity of unknown metabolites. Section 3.3 reports on ecotoxicity analysis of wastewater and surface water samples. Section 3.4 concerns antibiotic resistant bacteria (ARB); subsequent to our findings in the PILLS project (PILLS, 2012), concerns over ARB have received considerable attention in the press and in public policy. Wastewater, and in particular hospital wastewater, can be a significant source of multi-resistant bacteria (Stalder et al. 2013) and as such constitute a pathway for such organisms into the natural environment.

3.1.2 The sampling campaigns

This section focuses on the sampling campaigns in conventional wastewater treatment plants and surface waters. Hospital sampling campaigns were also conducted; these are mentioned below but reported on in full in Chapter 6.

In Germany, sampling took place at the influent and effluent of centralised WWTP Dülmen on 8 occasions, as well as upstream and downstream from the WWTP in the receiving water, the Tiberbach. A separate sampling campaign was carried out at the dedicated hospital wastewater treatment plant (HWWTP) Marienhospital, which is also described in full in Chapter 6.

In France, the participating HWWTPs is dedicated to Hospital Center of Alpes-Leman (CHAL France), whereas the WWTP treats effluent from the nearby urban area (Figure 3.1). The WWTP and HWWTP are on the same site and have a combined discharge into the river Arve. Influent samples were taken at the discharge of the hospital, from the effluent outlet of the HWWTP, in the urban sewer and after the urban WWTP. In addition, samples were collected from the River Arve upstream and downstream of the treated effluent discharge pipe. Samples were collected on three separate occasions: November 2013, and March & September 2014.

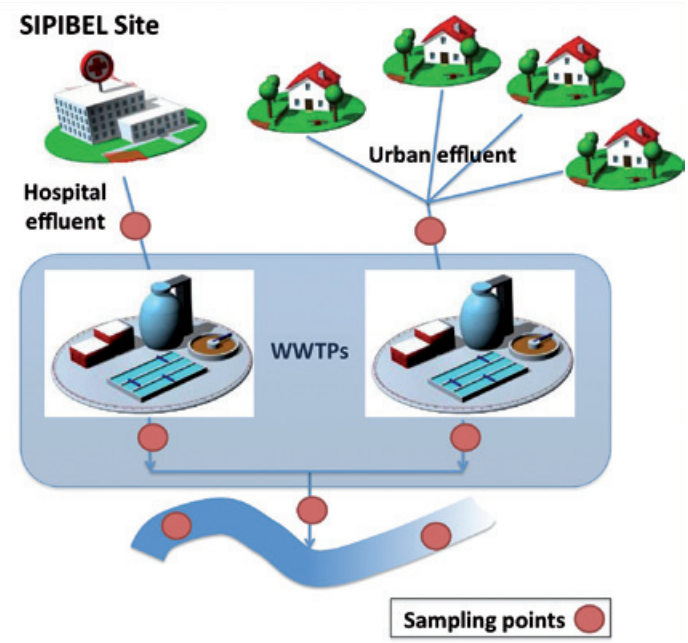


Figure 3.1: Location of sampling points at SIPIBEL Site

In Luxembourg, monitoring of wastewater at the partner hospital Centre Hospitalier Emile Mayrisch (CHEM) and the downstream municipal WWTP Schifflange took place over the time period of 28th April 2014 to 8th June 2014. It was implemented in parallel to a urine separation campaign in radiology department of the CHEM (see chapter 5). The time period was chosen because it was exclusively out of school holiday periods and standard working conditions were expected on the level of the radiology department involved in the urine separation campaign.

In Scotland, sampling took place at the influents and effluents of two WWTP, one using mainly trickling filter technology (TF) and one using mainly conventional activated sludge technology (CAS), and upstream and downstream in the receiving waters. For each WWTP, two 4-day sampling campaigns were undertaken, one in a dry week and one in a wet (rainy) week. In addition, samples were taken from 7 locations in the River Almond catchment on 4 consecutive days to gain an understanding of spatial variation in the catchment.

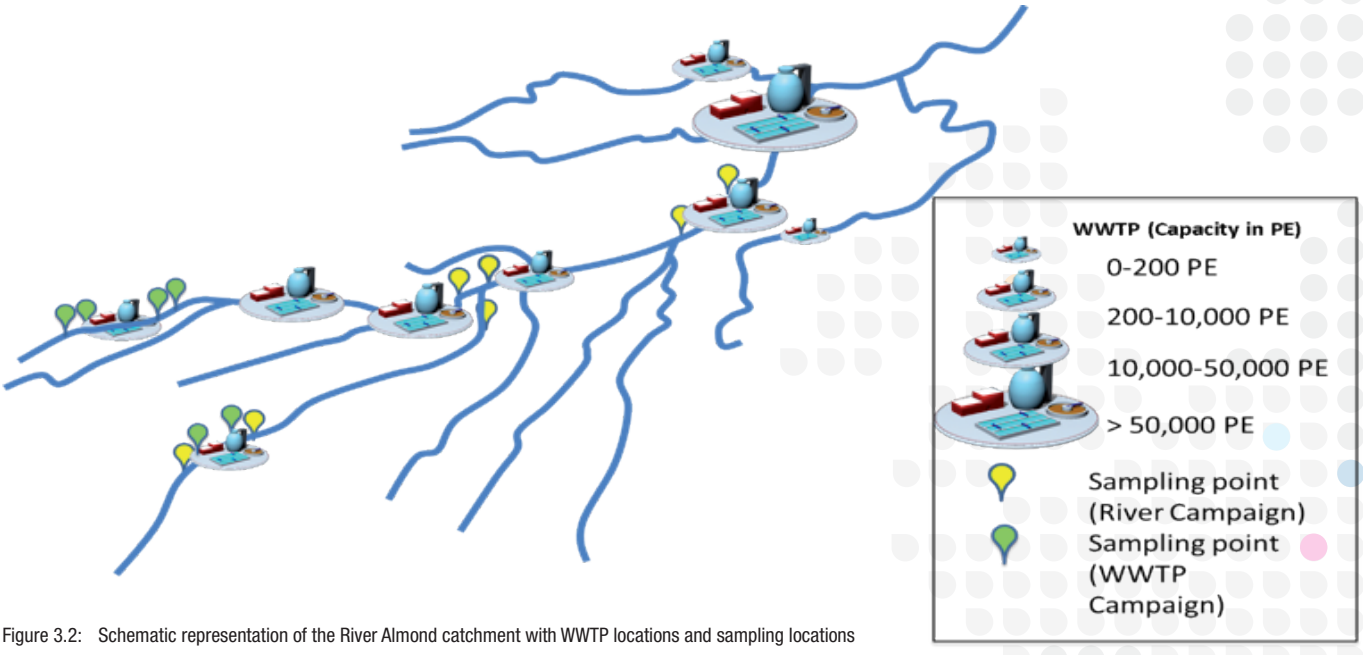


Figure 3.2: Schematic representation of the River Almond catchment with WWTP locations and sampling locations

Table 3.2 gives an overview of participating conventional treatment works.

Participating treatment works	Treatment technology
Luxembourg – WWTP Schifflange	CAS
Germany- WWTP Dülmen	CAS
Scotland – WWTP 1	TF (+ CAS as tertiary treatment for 20% of effluent)
Scotland – WWTP 2	CAS (+ TF as tertiary treatment)
France – WWTP SIPIBEL	CAS

Table 3.2: Participating conventional treatment works

3.2 Loads and concentrations in wastewater, treated effluent, surface water and sludge

3.2.1 WWTP influent and effluent concentrations

A number of pharmaceutical compounds were selected for transnational comparison of occurrence in various environments: atenolol, carbamazepine, ciprofloxacin, clarithromycin, diclofenac, erythromycin, ibuprofen, naproxen and sulfamethoxazole.

Comparing the range of concentrations found at influent and effluent (Figure 3.3), it can be observed that whilst in the influent the analgesics naproxen and ibuprofen dominate, in the effluent erythromycin and diclofenac are found in the highest concentrations. These two compounds also showed the most variation in removal efficiency between the investigated treatment plants. Most of the compounds investigated are present in effluent in ecotoxicologically relevant concentrations. The Predicted No Effect Concentration (PNEC) is a measure of aquatic toxicity and indicated by a red line for each compound in Figure 3.3. It should be noted that PNEC is not the only factor to be considered in determination of safe levels; other issues such as the potential to bioaccumulate and persistence in the environment are also relevant.

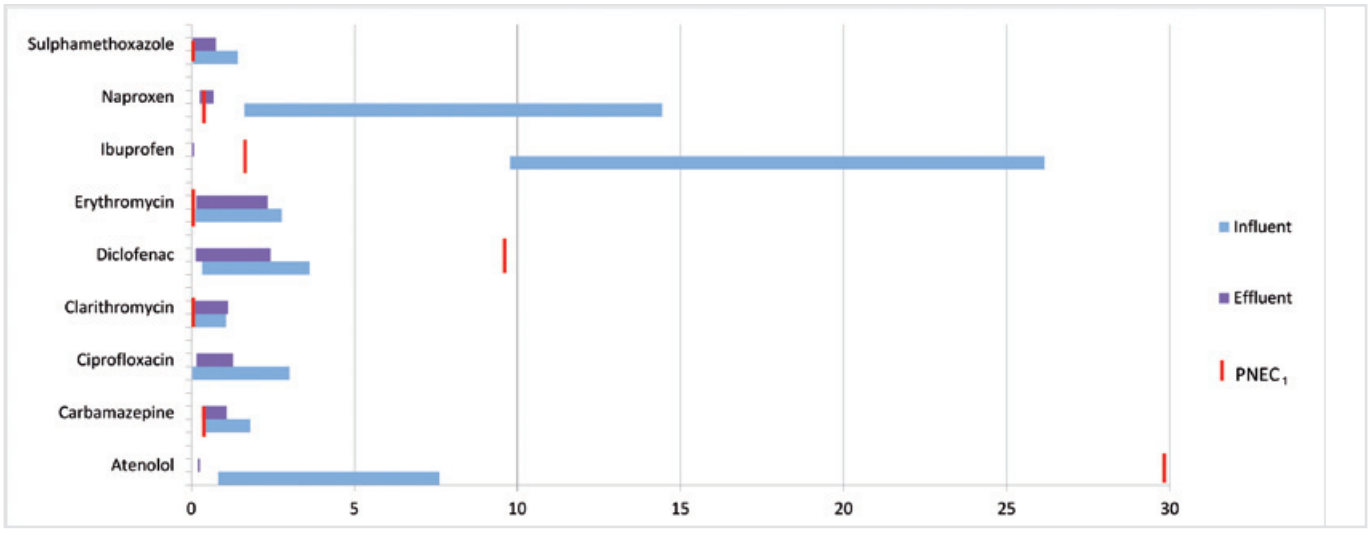


Figure 3.3: Range of influent and effluent mean concentrations (based on mean values at WWTPs in Germany, Luxembourg and Scotland) (µg/l), with indication of Predicted No Effect Concentration (PNEC). PNEC $_1$ values were taken from literature: Atenolol, Clarithromycin and Erythromycin from Boillot (2008), in Verlicchi et al. (2012); Diclofenac from Ra et al. (2008), in Verlicchi et al. (2012); Ibuprofen from Quinn et al. (2008), in Verlicchi et al. (2012); Naproxen and Sulfamethoxazole from FASS Allmänhet (2013); Carbamazepine from Ferrari et al. (2003); Ciprofloxacin from Halling-Sørensen et al. (2000).

A number of other interesting findings emerged:

- Investigating diurnal variation via analysis of two-hour composite samples over a 24 hour period, peaks in the load of specific pharmaceuticals received at a Scottish trickling filter plant (approx. 5000 population equivalent (PE)) appeared to correlate with the pattern of drug administration. A peak load was visible between 8:00 and 10:00 for atenolol, normally taken once a day, whilst three distinct peaks were observed for erythromycin, normally taken three times a day. Untreated, such diurnal variation in discharge rate could lead to short term peaks in river concentrations. However, unless combined sewer overflows are active, the treatment plant will act as a buffer and less variation is expected in effluent. Work on measuring diurnal variation in effluent is ongoing.

- In Luxembourg, amoxicillin, ciprofloxacin, clarithromycin, sulfamethoxazole, lidocaine, diclofenac, naproxen, carbamazepine, iobitridol and iodixanol were all found in every influent and effuent sample at WWTP Schifflange. Similarly, in Scotland, during the 4-day campaign, atenolol, carbamazepine, erythromycin, clarithromycin, lidocaine and Ranitidine were found in all influent and effluent samples at WWTP 1.

- In Scotland, cyclophosphamide, a cytostatic used in the treatment of cancer, was found in influent and effluent samples on one day of the sampling period, despite the fact that no hospital effluent is treated at the WWTP. Although cyclophosphamide is usually administered in hospital, patients will normally go home after treatment and therefore excrete the drug into community wastewater. Cyclophosphamide was not detected in the Scottish hospital wastewater samples during the PILLS project.

- In Luxembourg, for all the substances on the common partner list (amoxicillin, ciprofloxacin, clarithromycin, erythromycin, sulfamethoxazole, diclofenac, naproxen, carbamazepine) significant daily variations of concentrations were observed at all monitoring locations. For carbamazepine, the daily concentrations culminate in the highest concentrations at the end of the week. This is also the case for diclofenac on the level of the WWTP inflow. Although for the other substances clear daily variation of concentrations were observed, they have no recognizable recurring weekly pattern. The widest ranges from maximum to minimum concentration were observed for clarithromycin, diclofenac and naproxen in hospital samples and for amoxicillin and ciprofloxacin for the WWTP influent and effluent samples.

- Of the selected compounds, carbamazepine, lidocaine and clarithromycin are hardly removed in the WWTPs in the study. Erythromycin was moderately removed in the German WWTP but poorly in Luxembourg and Scotland. Diclofenac was moderately removed in Luxembourg and Germany, but somewhat better in France and Scotland. The common analgesics (paracetamol, ibuprofen, naproxen) were all well removed. Comparing removal efficiencies with values in a review paper by Verlicchi et al. (2012), values were generally in good agreement with the literature; however, atenolol and diclofenac were removed better than suggested by the literature whilst clarithromycin and amoxicillin were not removed as well as in previous studies. An overview is provided in Table 3.3, with literature values for comparison.

Poorly removed (<30%)	Moderately removed (30-70%)	Well removed (>70%)
Carbamazepine (18%)	Bezafibrate (61%)	Atenolol (38%)
Clarithromycin (40%)	Ciprofloxacin (70%)	Naproxen (73%)
Erythromycin (26%)	Diclofenac (29%)	Ibuprofen (87%)
Lidocaine	Sulfamethoxazole (52%)	Paracetamol (93%)

Table 3.3: Removal of selected pharmaceuticals in the investigated conventional WWTP (literature value in brackets; from Verlicchi et al., 2012)

Summary:

- Analgesics are generally well removed but, due to their high concentrations in raw sewage, may pose a problem in CSO situations where they bypass treatment.
- A number of other pharmaceuticals are not effectively removed by conventional treatment.

Policy pointers:

- Monitoring of sewage discharges, including those from CSO in wet weather situations, is recommended.
- Current levels of several pharmaceuticals, including macrolide antibiotics, in WWTP effluents in our study were well in excess of Predicted No Effect Concentrations and may pose ecotoxic situations in surface waters unless significant environmental dilution is available.

3.2.2 Concentrations in surface waters

The available dilution by the flow in the receiving water can have a critical effect on whether a discharge results in toxic situations in the river. In Germany, the concentrations downstream from the river were almost the same as the effluent concentrations, indicating the stream has a very low dilution capacity (around 1.2): the Dülmen plant is not the only source of pharmaceuticals in the Tiberbach and many compounds were detected upstream from the WWTP; hence, its capacity to dilute the concentrations in the effluent is limited. However, Erythromycin and Clarithromycin, two of the 'Watch List' compounds, were only detected downstream from the WWTP and for most other compounds downstream concentrations were at least an order of magnitude higher than upstream. Only Ciprofloxacin was not detected in the river at all.

In France, all pharmaceutical compounds analysed were found both upstream and downstream from the WWTP; as expected, concentrations downstream were higher than upstream. The data do not indicate the dilution factor as the ratio between measured effluent and river concentrations varies per compound.

In Scotland, the available dilution for WWTP 1 is low, but higher than in Germany; during dry weather, the dilution factor in Scotland was between 2 and 6. Mean (treated) effluent concentrations in wet weather were around half of those during dry weather and a higher dilution rate was also observed.

The dilution available at the investigated sites in Germany and Scotland is much lower than the default dilution factor of 10, used in the risk assessment method published by the European Medicines Agency (EMEA).

Most pharmaceuticals in rivers, measured in France, Germany and Scotland, are in the high nanogram range, but some – notably Erythromycin and Diclofenac – are present in higher concentrations (Figure 3.4). It is important to consider concentrations in the context of toxicity; especially antibiotics can be toxic at very low (0.05 µg/l) concentrations.

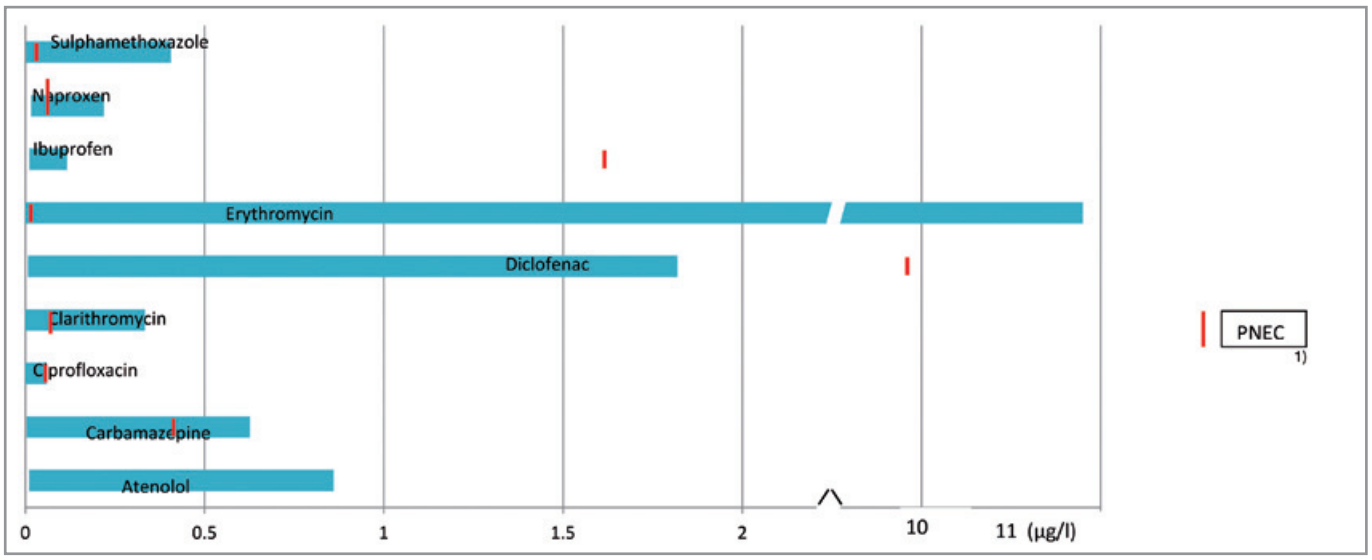


Figure 3.4: Range of mean concentrations in surface waters (based on mean values at single locations in Germany, Scotland and France; total 11 locations)
1) For PNEC value references, see figure 3.3.

The most extensive river monitoring work was carried out in Scotland. The River Almond (West Lothian) catchment is highly urbanised; the river and its tributaries receive effluent from multiple WWTP as well as numerous smaller discharges such as from septic tanks. To investigate spatial variation, daily grab samples were taken at seven locations in the upper and middle sections of the catchment. Eleven investigated compounds were detected at all but one locations, at concentrations mostly in the high ng/l range but up to 14 µg/l (erythromycin), indicating these compounds are ubiquitous in the catchment. Four of these, ciprofloxacin, ibuprofen, and the two macrolide antibiotics erythromycin and clarithromycin recently added to the Watch List were consistently found at toxicologically relevant concentrations in several locations. Some compounds were detected in a small tributary upstream from any WWTP input, and, comparing two locations 10km apart with no WWTP effluent inputs in between, several compounds were detected at similar or even higher concentrations at the location 10 km downstream. Although further research is necessary, these results suggest that non-WWTW discharges (e.g. septic tanks, veterinary sources) may not be negligible as contributors to overall levels of pharmaceuticals in this small stream.

For one location in Scotland, the daily load was calculated from measured concentration and flow, using NHS prescription data, taking excretion and removal efficiencies from literature (Table 3.4). Despite some limitations (removal values from literature were not available for TF technology so CAS removal efficiencies were used; measured values were based on grab samples only), measured values were within a factor 3 of predicted values.

Of all the WWTP discharging into the investigated parts of the catchment, only the furthest downstream receives hospital effluent. Despite this, there was no clear change in the range or concentrations of pharmaceuticals detected downstream from this WWTP compared to those detected in locations further upstream, which contain effluent from non-hospital sources.

	Expected daily load in river in the Breich Water tributary (downstream of WWTP), Scotland (mg/day)	Measured daily load (mg/day)
Atenolol	4404	3802
Bezafibrate	285	133
Carbamazepine	195	462
Clarithromycin	916	503
Lidocaine	nd[a]	216

Table 3.4: Comparison with predicted concentrations.
a: due to uncertainty over both the route of administration and the amount sold over the counter for Lidocaine, no predicted value could be calculated

Summary:

- Pharmaceuticals are ubiquitously present in the environment.
- Some, including macrolide antibiotics, are present in ecotoxicologically relevant concentrations.
- A clear increase in concentrations is observed after sewage effluent enters the river.
- The available environmental dilution is an important factor in the risk ensuing from effluent concentrations; where multiple discharges enter the same surface water the dilution capacity can be less than suggested by flow volumes.

Policy pointers:

- There are indications that non-WWTP sources may contribute significantly to pharmaceutical loads in the aquatic environment. Further research is needed to verify this and to determine the relevance of other sources, as actions to upgrade WWTP may not always be sufficient to protect the environment.
- As our measurements indicate that some of the macrolide antibiotics on the 'Watch list' are present in sufficient quantities to pose an actual environmental risk, more extensive monitoring of these compounds is recommended.
- Risk assessments should where possible consider realistic available dilution and take account of multiple inputs as cumulative loads.

3.2.3 Concentration in biological sludge and impact of stabilization treatment on the fate of pharmaceutical compounds in hospital sludge

Removal pharmaceutical in biological processes could be due to volatilisation, biodegradation and sorption on sludge. In this last case, pharmaceuticals are still present at variable concentration and could contaminate soils in case of agricultural application. Via soils, compounds could furthermore enter groundwater or surface waters (Lachassagne, 2014). It is then important to know the concentrations and the stability of pharmaceuticals during sludge stabilisation processes, before land spreading.

The behaviour of 11 pharmaceutical compounds was investigated during the treatment of sludge from hospital wastewater (SIPIBEL France): carbamazepine* (CBZ), ciprofloxacin* (CIP), sulfamethoxazole* (SMX), salicylic acid (SAL), ibuprofen (IBU), paracetamol (PAR), diclofenac* (DIC), ketoprofen (KTP), econazole (ECZ), atenolol (ATN) and propranolol (PRP). Thickened activated sludge was subjected to two different stabilisation treatments: anaerobic digestion and liming, before lab scale agricultural application (Figure 3.5). Modification of biochemical properties of sludge after stabilization are reported in Table 3.5.

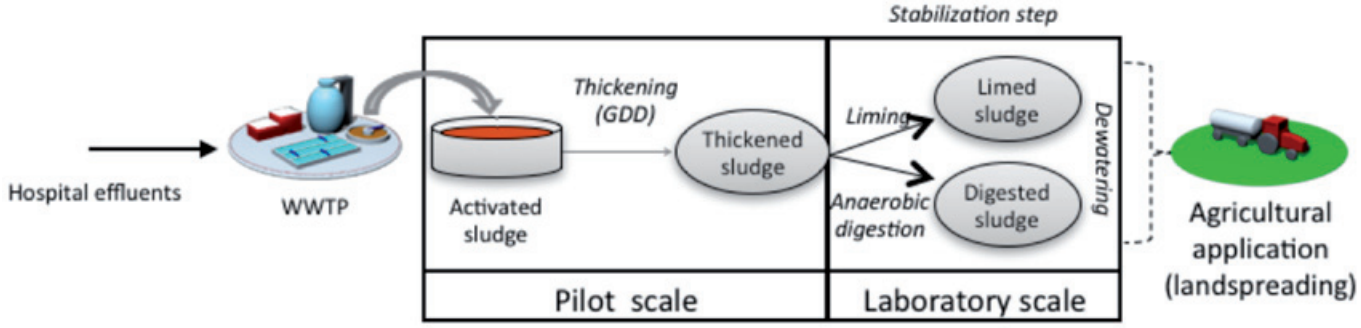


Figure 3.5: Different stages of hospital sludge treatment, stabilization and application (GDD: drip grid)

Liming	Anaerobic digestion
• The protein concentration is higher in the soluble fraction of the limed sludge, probably due to cell lysis of the microorganisms present in the sludge due to the pH increase taking place during the liming.	• Digested sludge was mainly constituted of humic-like substances. • The soluble fraction was mainly composed of carboxyl groups and the particulate fraction of phosphoric and amine groups. • Phase distribution of pharmaceutical compounds showed that carbamazepine and ibuprofen were mainly in the soluble fraction, so could be more available after landspreading. • Sulfamethoxazole was the only compound removed during anaerobic digestion.

Table 3.5: Summary of the effects of stabilization steps on biochemical composition of hospital sludge.

1 * noPills substances

Figure 3.6 shows that the concentrations of pharmaceutical compounds in the sludge after stabilization by liming or anaerobic digestion were very different depending on the specific compound. Whatever treatment applied, among these molecules, Ciprofloxacin had the highest concentration in the sludge, whilst econazole had the second highest concentrations. Ciprofloxacin concentrations are not shown; they vary between 4.05 and 1.5 during liming and between 4.05 and 1.0 during anaerobic digestion)

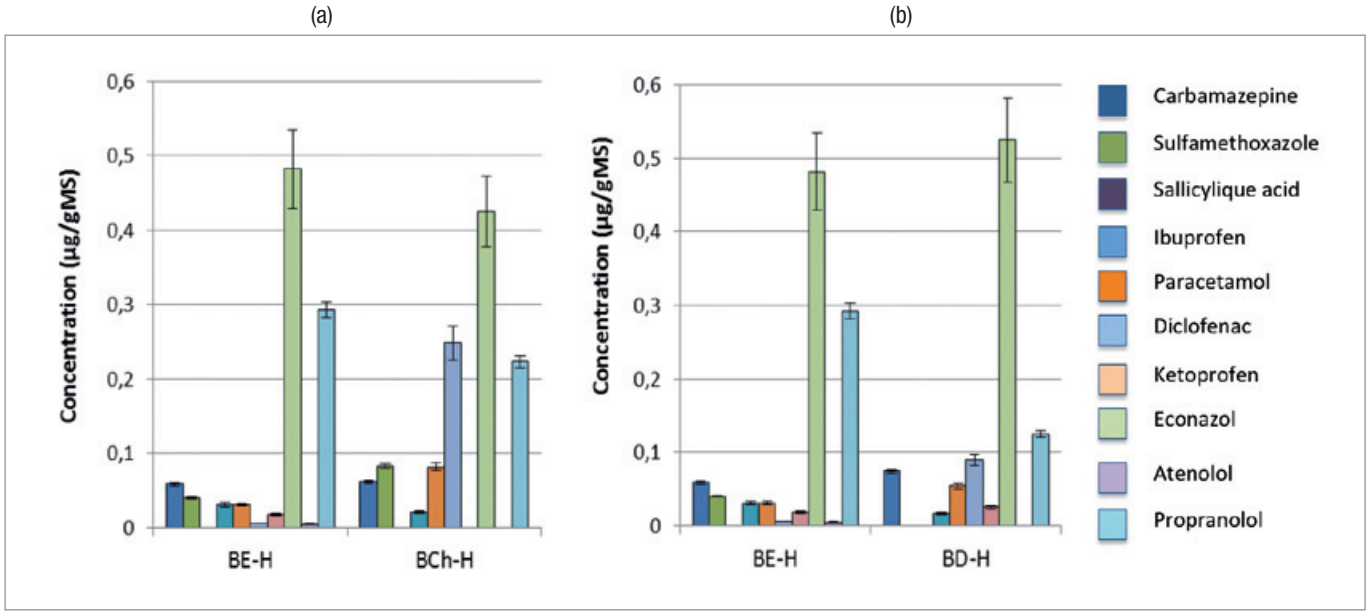


Figure 3.6: Evolution of pharmaceutical compounds concentrations during hospital sludge stabilization processes: liming (a) and anaerobic digestion (b). BE-H : hospital Thickened Sludge, BCh-H : Hospital limed Sludge, BD-H: Hospital Digested Sludge. The concentrations are expressed in µg/gTS.

Organic micropollutants behaviour during sludge treatment is linked to specific interactions between functional groups of sludge structure and those of the compounds. The pKa of functional groups such as carboxyl, amine, phosphate and hydroxyl characterises these interactions, which are partially responsible for the sorption of pharmaceutical compounds onto sludge.

Proton binding site concentrations and corresponding pKa values were assessed in soluble and particulate fractions by a combination of potentiometric tritrations. Activated, thickened, limed and digested sludges, showed four groups of pKa values in particulate and soluble fractions, which can be attributed to the following functional groups of components: pKa1 and pKa2 to carboxylic group, pKa3 to phosphoric group and pKa4 can be attributed to amine and/or hydroxyl groups.

The functional group distribution in the particulate fraction of activated, thickened and digested sludges was similar, except for the carboxyl group distribution which was lower for the particulate fraction of digested sludge. In the soluble fraction, the distribution of each group of components was different between the three kinds of sludge. Indeed, the distribution of carboxyl groups was less important for thickened sludge (10 %) than for activated (50 %) or digested (65 %) sludge. Regarding digested sludge, the distribution of carboxyl groups was more important in the soluble fraction. Carboxyl groups can be linked to proteins, humic-like substances and uronic acids. Amine groups were mainly present in proteins whereas hydroxyl groups originate essentially from polysaccharides and humic-like substances.

The two different stabilisation treatments have different effects on the partitioning of the pharmaceutical compounds in the sludge. The phase distribution of pharmaceutical compounds in soluble and particulate fractions of hospital sludge after stabilization was determined and presented in table 3.6. Sludge stabilization treatment (liming or anaerobic digestion) processes did not lead to a complete elimination of pharmaceutical compounds; only phase distribution of compounds changed between the two parts of the sludge during the treatment.

Compound	Limed hospital sludge			Digested Hospital Sludge		
	% particulate	% soluble	$Kd_{sorption}$ (L/kg)	% particulate	% soluble	$Kd_{sorption}$ (L/kg)
Carbamazepine	51.2	48.8	36.9	47	53	50.4
Ciprofloxacin	80.3	19.7	143	92.5	7.5	698
Sulfamethoxazole	100	0	8265[b]	N.d.[a]	N.d.[a]	N.d.[a]
Salicylic Acid	N.d.[a]	N.d.[a]	N.d.[a]	N.d.[a]	N.d.[a]	N.d.[a]
Ibuprofen	0	100	0	0	100	0
Paracetamol	100	0	4065[b]	100	0	2643[b]
Diclofenac	70.5	29.5	84	0	100	0
Ketoprofen	N.d.[a]	N.d.[a]	N.d.[a]	0	100	1193[b]
Econazole	100	0	42 465[b]	100	0	52 443[b]
Atenolol	N.d.[a]	N.d.[a]	N.d.[a]	N.d.[a]	N.d.[a]	N.d.[a]
Propranolol	100	0	743 298[b]	57.7	42.3	77.6

Table 3.6: Particulate-soluble pharmaceutical compounds repartition and Kdsorption values for limed and anaerobically digested hospital sludge
a: N.d = Not determined, because the compound was not detected in the total sludge
b: $Kd_{sorption}$ is maximum (even infinite). In those cases where the concentration in the soluble phase is less than the detection limit, the value of the detection limit was used for calculation.

Regarding phase distribution and stabilization process, different behaviours for all compounds are summarized table 3.7.

Liming	Anaerobic digestion
Pharmaceutical compounds were present at concentrations less than 0.5 µg/gTS with the exception of ciprofloxacin. Overall, liming causes a reduction of the drug content, except for sulfamethoxazole, diclofenac (hospital sludge) and econazole . Regarding phase distribution, differences in behaviour between all these compounds was observed. Carbamazepine was equally distributed in the soluble and particulate fractions of sludge. Paracetamol, econazole, propranolol and sulfamethoxazole were mainly in the particulate fraction, whereas ibuprofen was mainly in the soluble fraction.	The drug concentrations are less than 0.5 µg/gTS, except for salicylic acid which is present at a concentration of 1.2µg/gTS in urban sludge. Sulfamethoxazole was the only compound that was completely disappearing after anaerobic digestion while carbamazepine was still present after treatment. In digested sludge, all the ibuprofen was present in the soluble fraction. This compound could be more likely desorbed into the soil if the sludge is used for landspreading. Carbamazepine and propranolol were equally distributed between the particulate and soluble fractions, Ciprofloxacin, paracetamol and econazole were mostly in the particulate fraction, and ibuprofen, Diclofenac and ketoprofen were mainly in the soluble fraction.

Table 3.7: Impact of sludge stabilization treatment on pharmaceutical phase distribution

The organic compounds (in this case pharmaceuticals) are sorbed to sludge partly by hydrophobic type interactions, but mainly by electrostatic interactions. Microorganisms present in the sludge have a negative surface charge and act as cation exchangers, which causes a strong interaction between the micro-organisms' surface and positively charged compounds at the typical pH of sludge, such as carbamazepine or atenolol. However, it appears that hydrophobic interactions play a role for the positively charged compounds. In addition, at a typical pH for wastewater, compounds having a high log Kow, such as diclofenac and ketoprofen, are mainly negatively charged (ionized form) and will tend to be present in the aqueous phase, whereas compounds having a low logKow are mainly present in the particulate phase (Lachassagne, 2014).

In conclusion, hydrophobicity (log Kow) cannot by itself explain the sorption behaviour of sludge and the soluble / particle distribution of micropollutants. The functional groups present in sludge at each stage of processing also play an important role in the interactions.

Summary:

- Pharmaceuticals are partly sorbed to sludge by hydrophobic type interactions, but mainly by electrostatic interactions (Lachassagne, 2014).
- Stabilisation processes during sludge treatment could modify these interactions depending on the process. Molecules can then become available and can reach water bodies.

Policy pointers:

- Potential contamination of sludge during biological treatment and stability of sorption has to be considered in the overall balance of removal and in decision making on the use of sludge.

3.3 Environmental ecotoxicity evaluation

3.3.1 Introduction

When chemical compounds are developed to enter the EU market, their potential fate and effect in the environment is assessed under the EU REACH regulation. The testing is focused on evaluating the toxic effects on humans and ecosystems, and their fate in the environment: persistence and bioaccumulation in the food chain. When chemicals are very toxic, or are not degraded in the environment, leading to increasing environmental concentrations, or when they accumulate in the food chain, leading to high concentrations in the top predators, measures to prevent release of the chemicals into the aquatic environment may be required or the marketing authorisation can be denied. As some of the most potent pharmaceuticals may be used in low doses, total tonnage may be below REACH thresholds. Furthermore, if an environmental risk for pharmaceuticals is identified, certain mitigation proposals may be required, but a marketing authorisation will not be denied (BIO Intelligence Service, 2013). Pharmaceutical residues enter the environment, either as a result of excretion from the human body, or as a result of discharge of medicine waste, and can include very toxic (e.g. cytostatics) or very persistent (e.g. X-ray contrast agents) compounds.

Although pharmaceuticals are produced to heal humans, Paracelsus knew already in the 15th century that "Dosis facit venenum", "The dose makes the poison". If the concentration of a medicinal compound in a body is too high, it will act as a toxic compound. This is the same in the environment where the wide range of creatures exposed will respond differently, thus it is important to evaluate the toxicity of pollutants or polluted environments with a range of test organisms. We know that the toxic dose of one compound for different environmental organisms may vary by more than a factor 1000; in general smaller organisms are more sensitive than bigger organisms due to their larger surface-to-volume ratio. When determining the environmental toxicity of a drug the mode of action should also be considered as the target receptors and enzymes may affect different species in different ways. Furthermore, the effects of long term exposure to a compound may appear at lower concentrations than a one-off exposure to a high environmental concentration that disappears quickly.

Whole sample ecotoxicity testing exposes test organisms to the mixture of all chemicals present in the sample. Toxicities of individual compounds may be synergistic or antagonistic; whole effluent toxicity is almost impossible to predict as an ever-changing mixture of thousands of compounds is present in sewage effluent. Mixture toxicity has been investigated for few compounds only (e.g. Christensen et al., 2007; Cleuvers, 2004). Ecotoxicity testing as described below therefore offers vital complementary data to the chemical analytical data on single pharmaceutical concentrations.

3.3.2 Ecotoxicity testing

The ecotoxicity of collected wastewater samples was assessed using a battery of tests (Table 3.8).

Country/ Evaluation	Scotland		France	
Acute toxicity	Bacteria Algae Fish	*Aliivibrio fischeri* (ISO 1348-3) *Raphidocelis subcapitata* *Danio rerio*	Crustacean	*Daphnia magna* (ISO 6341)
Chronic toxicity	Fish	*Danio rerio*	Algae Crustacean Rotifer	*Pseudokirchneriella subcapitata* (ISO 8692) *Heterocypris incongruens* (ISO 14371) *Brachionus calyciflorus* (ISO 20666)
Genotoxicity			Bacteria Mammalian cells	SOS chromotest single cell comet assay
Mutagenicity	Fish	*Danio rerio*	Fish	*Danio rerio*
Endocrine disruptors			Human cell line	Estrogenic activity (MELN cell line)

Table 3.8: Test organisms utilized during the evaluation of wastewater samples plus relevant ISO standard followed or in-house protocols followed.

3.3.3 Outcomes

Scotland

Of the 99 samples evaluated using the inhibition of *Aliivibrio fisheri* luminescence, 45 % were defined as acutely toxic and 55 % as not acutely toxic (i.e. where there was no decrease in relative light units after 30 mins). The maximum inhibition recorded was 28 %, in WWTP influent. Thirty five percent of the samples were considered as toxic to *Danio rerio* embryos as judged by mortality (Table 3.9). Pre-concentration of the samples utilizing freeze-drying as the enhancement step continues to be investigated. Toxicity evaluation utilizing algae is still on-going.

Location	**Luminescent bacteria** *(Aliivibrio fischeri)*	**Zebrafish** *(Danio rerio)*
River	21.9	21.9
WWTP Influent	72.7	45.5
WWTP Effluent	36.4	36.4

Table 3.9: Percentage of samples defined as being toxic to the test organism. Collated data for 2 treatment works, $n_{total} = 11$.

Of the two WWTP's monitored, the trickling filter treatment facility yielded the largest number of acutely toxic samples compared with the activated sludge treatment facility (Table 3.10). This observation can partially be accounted for the increased toxicity of the influent samples reaching the trickling filter facility compared to those entering the activated sludge treatment facility.

Primary sewage treatment	**Sampling Location**	**Number of samples (n)**	**Luminescent bacteria** *(Aliivibrio fischeri)*	**Zebrafish** *(Danio rerio)*
	Weather condition: low rainfall (total 5.6mm TF; 5.5mm AS during campaign)			
Trickling filter	Influent	4	100.0	25.0
	Effluent	4	50.0	50.0
Activated sludge	Influent	3	33.3	0.0
	Effluent	3	0.0	0.0
	Weather condition: high rainfall (total 9.1mm TF during campaign)			
Trickling filter	Influent	4	75.0	75.0
	Effluent	4	50.0	50.0

Table 3.10: Effect of treatment within WWTP and of rainfall on samples defined as being toxic to the test organism (percentage of samples).

France

A range of ecotoxicity assays were used to characterize the environmental impacts of a samples entering and leaving the WWTP associated with the monitored hospital (Table 3.11). The toxicity of the hospital effluent changed with time, with the spring 2014 sample being considered the most toxic. The whole organism toxicity (either acute or chronic) and the endocrine disruptor evaluation appeared to be the useful measures, however, to characterize the environmental impacts of a sample of water a battery of assays are required. A major reduction in the ecotoxicity of the effluent was noted after treatment.

Assessment	Outcome measure	Hospital effluent	After WWTP	Hospital effluent	After WWTP	Hospital effluent	After WWTP
		November 2013		March 2014		September 2014	
Acute toxicity							
Crustaceans *Daphnia magna*	EC_{50} (%)	56.6	>90	8.3	>90	56.6	>90
Chronic toxicity							
Freshwater Algae *Pseudokirchneriella subcapitata*	EC_{20} (%)	19.9	>80	15.7	68.7	19.9	>80
Rotifer *Brachionus calyciflorus*	EC_{20} (%)	61.5	100	6.8	100	61.5	100
Ostracode *Heterocypris incongruens*	Growth inhibition (%)	39.9	0	59.0	0	39.9	0
Genotoxicity & Mutagenicity							
Comet assay	Tail DNA (%)	NS	NS	NS	NS	NS	NS
SOS chromotest	Induction factor	2.0	1.5	1.7	1.8	2.0	1.5
Micronucleus	number of nuclei	14.0	1.7	25.0	4.0	14.0	1.7
Endocrine disruptors							
Thyroid hormone	ng/l EqT3	NS	NS	NS	NS	NS	NS
Estrogens	ng/l EqE2	30.5	0.14	14.0	0.12	30.5	0.14
Estrogens	ng/l EqE2	30.5	0.14	14.0	0.12	30.5	0.14

NS:- not significant

Table 3.11: EC50 concentrations indicating ecotoxicity of the hospital effluent before and after the WWTP (as percentage of the concentration measured in the sample)

The tests used were not sensitive enough to measure neither the background toxicity nor the impact of the effluent in the river Arve due to dilution of toxic compounds. Only the assessment of the chronic ecotoxicity using ostracode and rotifer and the evaluation of the endocrine disruptors yielded measurable results during two of the three monitoring periods.

Summary:

- Conventional WWTP are effective in reducing ecotoxicity levels but some toxicity remains.
- The most toxic WWTP effluent was that of the Trickling Filter plant. This may be partly ascribed to high influent concentrations.
- Over 20% of Scottish river samples were acutely toxic to aquatic organisms, indicating high pollution levels. However, it must be noted that it is not certain that the toxicity is due to pharmaceutical content.

Policy pointers:

- Research into the pharmaceutical contribution to toxic effects in surface waters is recommended.
- Research on ecotoxicological tests has to be improved to define the most relevant environmental impact(s) for monitoring.
- It is recommended that ways to assess whole effluent ecotoxicity (such as e.g. via biomarkers), should be considered for possible future standards, in order to account for full complexity of the mixture.

3.4 Antibiotic Resistance

3.4.1 Introduction

The discovery and use of antibiotics in modern medicine has undoubtedly contributed to the increase in life expectancy observed in the latter part of the 20th century. However, from the 1940s, the first cases of resistant strains were identified (sulfonamides 1939, penicillin 1941). The occurrence of these strains has resulted in the design of new molecules, but this forward march reaches its limit with the increase of resistant bacteria. The consequences are increased morbidity and mortality (estimated 25,000 deaths / year in Europe) but also the associated costs (additional cost 1.5 billion € / year) (Chomarat et al. 2014). Thus, control of antibiotic resistance in hospitals as well as in the community, has become a priority issue in public health in many industrialized countries and a priority for the World Health Organisation (WHO, 2015).

The emergence of antibiotic resistance phenomena is related to adaptive pressure process of germs to the presence of antibiotics. These phenomena are mostly due to horizontal transfer of genes, by exchange of mobile elements (plasmids, transposons, integrons) (Stokes and Gillings, 2011; Buckley, 2009) and via different phenomena (transformation, conjugation, transduction). This horizontal gene transfer probably occurs in all terrestrial ecosystems colonized by bacteria.

In recent years, particularly since the end of the European research program "Pills", the consideration of resistant bacteria carried by wastewater effluent, even treated, or hospital effluents, increased, with concern about the dissemination of bacterial resistance, and gene transfers that may accompany it. A significant number of publication states the presence of the Antibiotic Resistant Bacteria (ARB) along an aquatic continuum or watershed (Allen et al., 2010; Baquero et al., 2008; Wright et al., 2007; Schwartz et al., 2003; Novo et al., 2010).

The results in this study come from French locations. Antibiotic consumption in France remains above average in Europe and the United States. Between 2000 and 2013, antibiotic consumption declined by 10.7%, but increased by 5.9% since 2010 with 32.3 Defined Daily Doses /1000 Inh/Day. In terms of volume, over 90% of consumption of antibiotics is in the community and slightly less than 10% in the hospital. Exposure to antibiotics is high hospitals; on any given day about 4 out of 10 patients receive a dose of antibiotics (ANSM- French National Agency for Medicines Safety, 2014).

3.4.2 Determination of Antibiotic Resistant Bacteria

One of the difficulties in the analysis of antibiotic resistance is the choice of the method of determination, and, especially as the matrix in which occurs this research is complex (e.g. effluents, manure, soil). It is now recognized, and Pills program has contributed to this, that the search for Resistance Integrons (RI) is an approach contributing to an overall reliable and relatively simple estimation of antibiotic resistance. RI are genetic elements involved in acquisition, storing, and expression of antibiotic resistance genes embedded within a gene cassette, composed of a intI gene encoding an integrase protein, a specific recombination site attI, and a promoter, Pc. These RI are not self-transposable elements but are often located on plasmids or transposons, which promote their dissemination among bacteria.

Thus, the assessment of the amount of integration (concentration or relative abundance) is able to quantify and/or qualify the occurrence of antibiotic resistance, by molecular biology methods. The quantification of integrons was done in the same manner and with the same developed method as in Pills project (PILLS, 2012; Stalder et al., 2014).

All results are expressed either in concentration, representing the prevalence of RI in a given bacterial population, or in relative abundance, corresponding to the RI concentration divided by the estimated number of bacteria (calculated by dividing the number of 16S-rRNA-encoding gene per the average quantity of 16S-rRNA-encoding-gene per bacteria (4.1 gene per bacteria)).

The different samples collected from the different sites during the Pills and noPills programs clearly showed the specificity of hospital effluents compared to urban effluent, to other anthropic effluent, and to natural water (figure 3.7B). This is especially true if we consider the Relative Abundance (figure 3.7A).

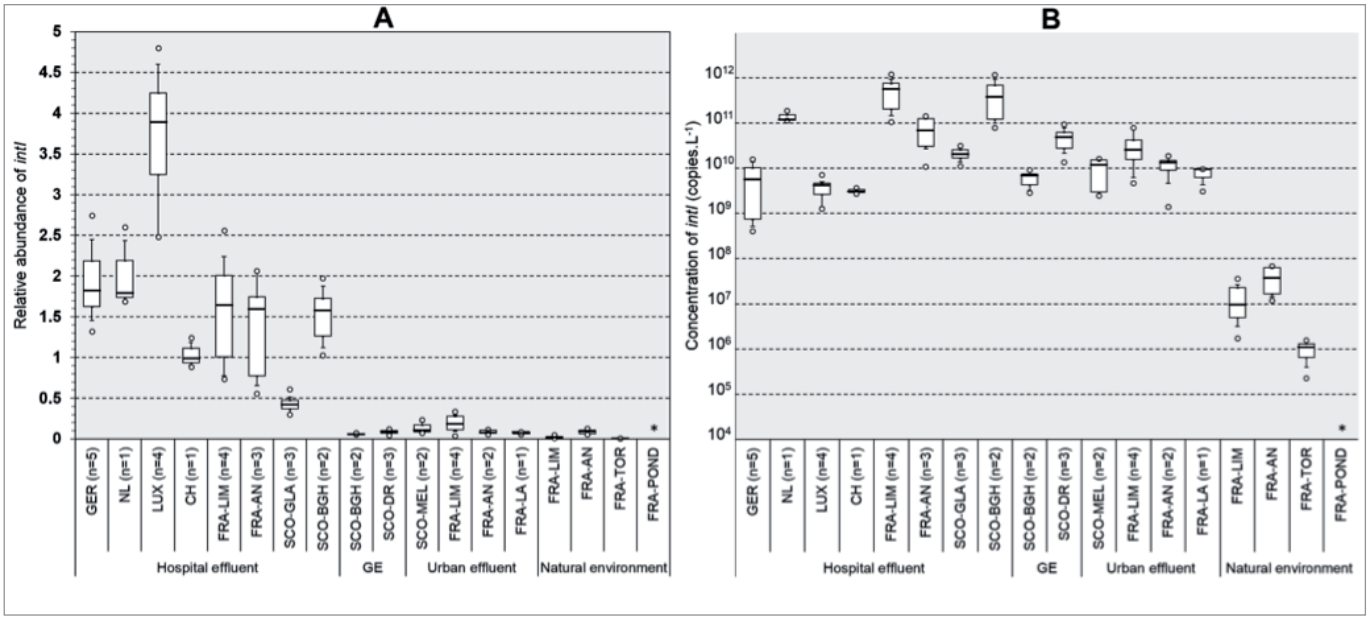


Figure 3.7: Relative abundance and concentration of Resistance Integrons in various samples (GER Germany, NL Nederland, SCO Scotland, FRA France, LIM Limoges, AN Annemasse, GLA Glasgow, TOR River.

3.4.3 Monitoring ARB

The pilot site of Bellecombe (SIPIBEL)
Located on the department of Haute-Savoie (Figure 3.8), near the Swiss border, the pilot site (described in Chapter 3.1) consists of:

- The Hospital Center of Alps Leman (CHAL) commissioned in February 2012, with a capacity of 450 beds;
- A wastewater treatment plant (WWTP) of Bellecombe with two separate processing lines one for the urban effluent, one for the CHAL, closed to the WWTP;
- A receiving water: Arve River, which supplies water for human consumption in Geneva.

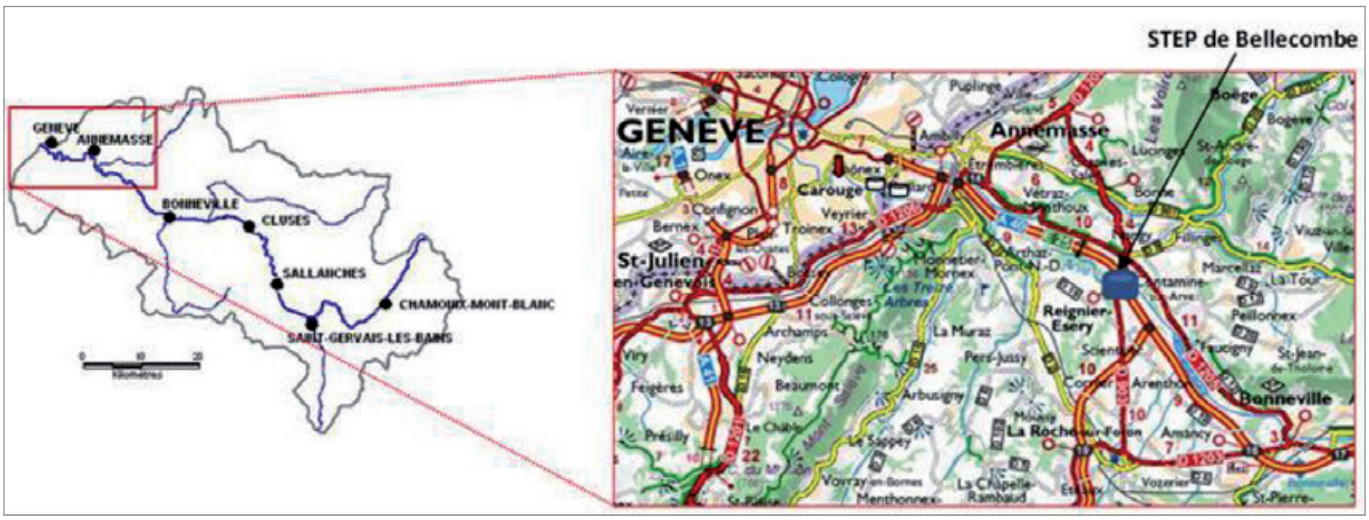


Figure 3.8: Localisation of SIPIBEL

A biological treatment system of activated sludge for 5400 population equivalent (PE) is dedicated exclusively to the treatment of hospital wastewater.

Prior to the opening of the facility in 2012, effluent samples discharging into the river were analysed.

Dynamic evolution on the investigated catchment area

Resistance Integrons (RI) were monitored and Relative abundance (RA) calculated during 3 years on SIPIBEL. Regarding the relative abundance, the cumulative results showed that:

The RA in the effluent discharged by the hospital was significantly higher than those of the urban effluent (figure 3.9), however the data was highly variable.

As in the last study, RA in urban wastewater was very low and statistically equal to those of the river, even downstream.

The wastewater treatment plant treating the hospital effluent showed a significant decrease in RI. This is likely due to a conventional removal of the number of bacteria (2-3 log), but for hospital effluent, these bacteria were multi-resistant.

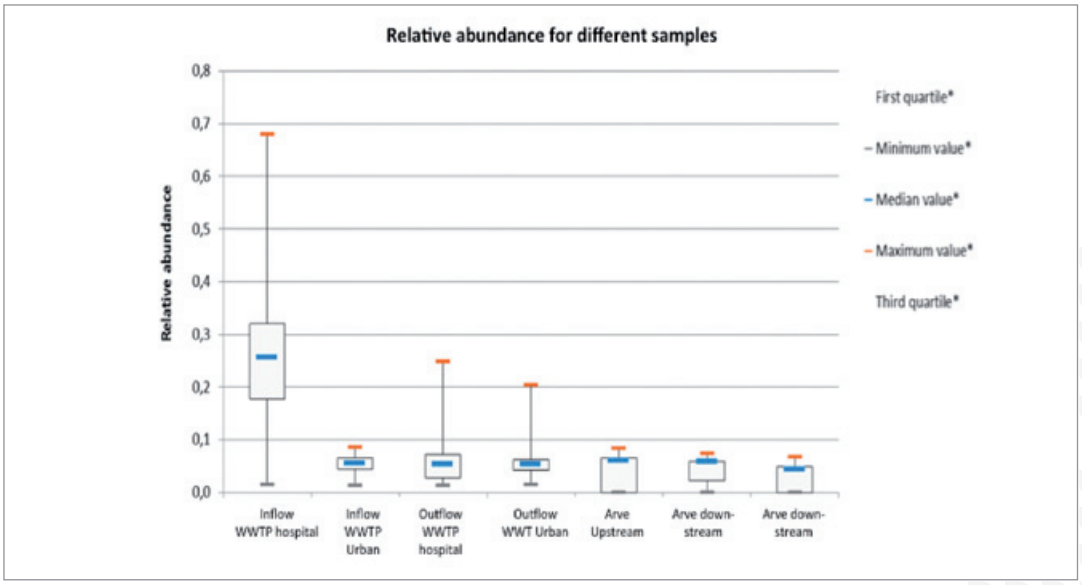


Figure 3.9: RA in different samples: influent and effluent of the urban and hospital WWTPs and Arve river.

The Bray-Curtis similarity index was used to analyse qualitatively the similarity between samples in terms of both gene cassette diversity and gene cassette arrays. We found (Figure 3.10) that the urban effluent and WWTP influent were most similar, while the hospital effluent and the recirculation sludge exhibited very specific patterns, showing the specificity of hospital effluent in term of resistance to antibiotics.

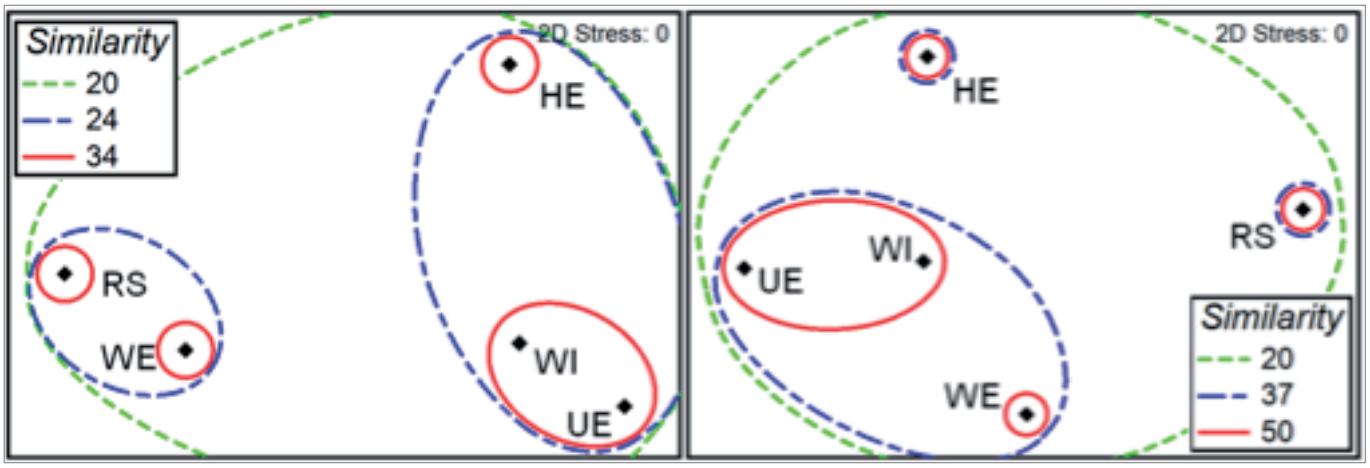


Figure 3.10: Index of Bray-Curtis for (A) the gene cassettes diversity, and (B) the gene cassettes pool. UE, urban effluent, HE hospital effluent, WI, influent WWTP, WE effluent WWTP, RS, sludge.

The evolution of RI and RA in the hospital effluent before and after treatment is reported in Figure 3.11 and compared to the urban effluent at the same time, and over a three year period.

It is noted that the evolution of RI and especially of the RA is constantly higher in the effluent from the hospital than in the urban effluent. It is confirmed that the output values of the two treatment plants, urban or hospital, are

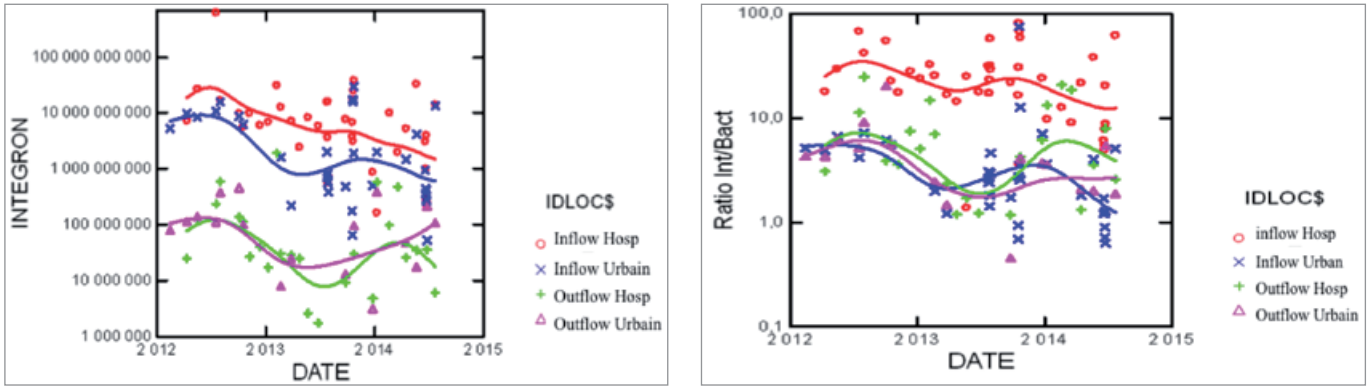


Figure 3.11: Concentration of RI (2) and RA (1) during the noPills Programme

statistically comparable during the entire time of the experiment. One diminution is relatively standard compared to the bacterial elimination in a WWTP (2 to 3 log). The number of RI spread into the environment from a wastewater treatment plant is approximately proportional to the bacterial content and similar between hospital and urban effluents.

Summary:

- Sewers collect wastewater, which comes from homes or care centres, and may contain a resistant bacteria load. The relative abundance of resistant bacteria in a hospital effluent is higher than in an urban effluent.
- The quantification of integrons and relative abundance could be a method to evaluate an overall resistance before a specific identification with molecular technique.

Policy pointers:

- The fight against antibiotic resistance requires a range of approaches, which could include:
  - The standardization of quantification methods
  - The definition of indicators to monitor ARB –such as integrons used in this study
  - The definition of a methodology for risk assessment
  - The evaluation of gene transfers in anthropic systems
- Control of resistant bacteria at source could play a role in maintaining effectiveness of antibiotic treatments.
- Fundamental research of resistant bacteria and gene transfer is recommended.

3.4.4 Concluding remarks

Worldwide, national governments have embarked on numerous initiatives to reduce risks from antibiotic resistance, e.g.:

- French 'Roadmap 2015' of the Ministry of Ecology "…on reducing health risks by assigning a expert mission to ANSES (French Agency for Food, Environmental and Occupational Health & Safety)
- French Ministry of Health coordinated the preparation of a technical guide "for waste management (from drugs – liquids) by the health and social service institutions" to be published in 2015.
- UK Department of Health Antimicrobial stewardship initiative (DOH, 2011)
- Key measures proposed by the European COST TD 0803 (see Berendonk et al, 2015)
- The United States of America proposed "a national action plan for combating antibiotic-resistant bacteria" (TWH, 2014)
- At EU level, macrolide antibiotics have been added to the 'Watch list' (erythromycin clarithromycin, azithromycin) (European Commission, 2015)

Areas of research and development include the development of rapid diagnostic techniques, the development of new antibiotic drugs, improvements in waste and wastewater management, and understanding and control of pathways of resistance. Many initiatives have been undertaken, but given the potential crisis to come, much research and development remains to be done to protect public health.

4 Reducing the pharmaceutical load at source: engaging society about pharmaceutical consumption and disposal

4.1 Introduction

Reducing the pharmaceutical load entering the sewer can reduce the need for technological solutions such as advanced treatment technologies, which are expensive and energy intensive. Unlike advanced treatment technologies, it would also address the fraction of wastewater discharged via combined sewer overflow (CSO). Attitudes and behaviour around the prescription, consumption and disposal of medicines might play a significant role in such a reduction, whereby the awareness of the general population and of a number of key stakeholders for example medical professionals might play an important role.

4.2 Chapter structure

This Chapter describes the engagement-research activities, primarily with members of the general public in three case-study countries (France, Germany and Scotland) but also, to a degree with some key stakeholders in two partner countries: Germany and France. Key themes addressed in each activity are (patterns associated with) consumption of prescribed and over-the-counter (OTC) medicines, disposal, attitudes to stakeholders, attitudes to health, and awareness of (associated) environmental issues. As different methodologies were applied specific to the respective research objectives, results are not directly comparable; therefore, the chapter maintains the case-study approach with individual methodologies explained in each respective case. Key findings from across the project are integrated into a concluding paragraph. The activities generally sought to develop understanding of the societal context of medicine use and to identify 'policy pointers': for example including potential levers to engender behaviour change or to raise levels of awareness.

4.3 Scotland – public attitudes to medicines: consumption, storage and disposal

To the extent that members of the public might have a central role in reduction of pharmaceutical residue in water, this lies in two areas: their use / consumption of medicines and then their disposal behaviours. Consequently, the project aimed to capture the public awareness in a baseline assessment of behaviours and experiences (i.e. attitudes, beliefs and practices) on the issue of pharmaceuticals, through a qualitative inquiry. The Scottish component consisted of two phases. In Phase 1, 102 interviews in a conversation format were carried out during 2014, in 5 communities in both rural and urban localities, covering varied socio-economic settings. Participants were recruited via local press, posters in the community and 'word-of-mouth', as well as directly through community organisations and community centres.

In Phase 2, workshops were held with residents of the same five communities. Objectives for the workshops were:

- to explore notions of risk and safety both for consumption and disposal of medicines,
- to gauge awareness of environmental issues around pharmaceuticals and
- to assess notions of stakeholder responsibility amongst the participants as well as explore realistic adaptations to use and disposal behaviours.

Analysis was undertaken using Nvivo software with an aim to explore the current practices – attitudes and experiences of pharmaceuticals.

The following themes emerged as the central considerations those we interviewed, drew attention to:

- Complex attitudes and behaviours towards medicine use
- Multi-faceted approaches towards decision making and advice or information sourcing about the use of medicine
- Varied behaviours around storage and disposal of medicines

4.3.1 Attitudes to medicines: behaviours and consumption practices – evidence from interviews

Cautious approaches towards medicines and their use

When we look at the evidence from interviews with participants we see a complex 'relationship' with medicines. Most interviewees expressed a degree of apprehension both about medicinal use in general and particular ones specifically. For some this is because as prescribed products they might be seen as potentially more dangerous, but also borne out of potential interactions between drug combinations and potential side effects. "I definitely do not want to be ... seen as someone who takes drugs."

As a result this caution has clearly impacted upon individual behaviours, wariness leading some to stop taking the (prescribed) medicine and: "…learned to live with… the pain" in this case because it was better than being "a total zombie". For some there was a view that 'other people' take too many drugs or are too ready to do so, partially explaining their own reluctance: "… I know a lot of people take a whole line of pills every day… but I would be cautious…"

Self-medication and approaches towards over-the-counter products

This complexity in relation to medicine use is highlighted in some perceived views on OTC product (use). Amongst some respondents there does seem to be a relaxed approach to some OTC products and supplements. This appears to be based on the fact that OTC products, given their more general availability, are presumed to be safer. In one extreme case for example, a pharmaceutical lozenge product, for easing throat discomfort, was described as "sweets" (a confectionary).

Often OTC products appear to be used "...so you don't need to talk to the doctor..." This is particularly interesting in the Scottish case as prescribed products carry no direct cost to the patient whilst OTC products are paid for by patients directly. It was commonly identified by individuals that they make use of OTC products, particularly for simple ailments, as their need determined. For example, some recognised medicinal guideline (limits) but were sometimes prepared to relax this in their own use. There is evidence that even though some respondents have a very detailed knowledge of dosage information and levels to be used, on occasions, they choose to ignore these. One respondent noted the restriction for ibuprofen: "… six in twenty four hours, [but] sometimes I would take eight." However one mother noted that with respect to administering medicines to her children: "I …follow the instructions absolutely to the letter… I'm so frightened of doing something that would harm them…"

Side-effect awareness and knowledge

Not all interviewees appeared to be concerned with side effects "No, in general I am not worried about side effects." There are indications that those who had concerns often had a long-term pattern of use with (particular) medicines or use by family or friends. Consequently shared information through these sources clearly impacted upon their caution about use, with respondents often reporting the apparent impact of named drugs and very specific (for example: "horrendous") side effects. Some speculated on the long-term impact: "…somebody like myself who has been taking [named product] for ten years that's a long time. But what's the impact of taking it for thirty years, or forty years?"

Conclusion

We sought not to prompt interviewees to address highly specific questions; however there was one exception to this, as a concluding aspect to the interview we asked respondents to ponder whether as a society they thought we 'take too many medicines'. In no case did interviewees disagree with this. It is clear that in prior questioning many interviewees raised this issue either explicitly or obliquely. There is clearly an appetite for an agenda which would see the reduction in medicine use, though it needs to be said often this was formulated as a problem caused by 'other people' (making unnecessary demands on the system).

Summary:

- In general, a picture emerges that suggests people would prefer to take no more medication than they 'need' and that a certain wariness over taking 'too many' drugs exists. This cautiousness extends to (and can be even stronger when relating to) dependants in their care, for example children or elderly relatives.
- This is contrary to the sometimes (popularly) voiced opinion that people expect and want medication and might support a 'minimal prescribing regime'.
- There are conflicting associations between medicines and broader perceptions of 'care'; there are indications that policies delivering care without resorting to medicines could be further explored.
- There appears to be a view that 'society' is over 'medicinalised'.
- There appear to be complex and varied understandings of 'risk' and safety with respect to medicines partially indicated by differing attitudes to self-medicating: this may be worthy of further investigation.

Policy pointers:

- There would appear to be an appetite, by members of the general public, as potential patients, for an agenda that seeks to reduce medicinal input – policy might address this be encouraging alternative forms of appropriate therapy.
- It may be useful to investigate further the effect of changing a medicine's licence from 'Prescribed Only' to 'Over the Counter' on consumption behaviour, such as exceeding the recommended dose, due to perceived safety implications.
- Access to repeat prescriptions may lead to stocking up on medicines and, in some cases, to unauthorised distribution.
- Use of OTC medication apparently contrary to recommendations was relatively common; examining ways to address this issue could benefit both treatment outcomes and environmental outcomes.

4.3.2 Decision making influences – information sources and professional advice

A key aspect to pharmaceutical behaviour is the decision-making process which members of the public engage in when they 'choose' how to address a health issue. Of course overlain with that is one which determines whether they seek professional medical advice, or whether as a first line of action they choose to self-medicate or obtain other OTC products (etc).

Cost

For some a significant consideration in their decision making was cost – in Scotland this has specific reference only to OTC products as prescribed drugs have no direct cost to the consumer as we have indicated. Often participants drew attention to using supermarket own brand OTC products, for example with respect to cough remedies: "... XXX's [store's name] own brand contains the same ingredients as one that's prescribed on the NHS. I wouldn't go to a doctor... so I tend just to go to XXX and buy it. I've used it before and it's extremely effective". However some cautioned against this: one drew attention to a pharmacy (chain) own brand of asthma spray which was: "slightly inferior... I was choking; it wasn't having the same effect."

Effectiveness of medicines

Participants appeared to have a sophisticated sense of what works (personally) for treating a given condition or health issue. This was often based upon their own trial and error, particularly if it has been a repeating health condition or one that has been long term. Some took their own unilateral action taking a prescribed medicine once, experiencing an immediate and disturbing reaction and simply never using the medicine again: "…an hour and a half later I felt dizzy and sick and thought I was going to topple over so that was the last time I took that…"

Ethical considerations

Some respondents noted they were concerned to know what the composition of medicines is – particularly where they had ethical concerns; notably whether products are tested on animals.

Knowledge, information seeking and associated decision making

A crucial aspect to the consumption of medicines and the development of associated attitudes to their use, is the decision making strategies consumers adopt and the information sources they access for this. A range of factors come into play when individuals are seeking information on medicine use including: severity of condition, previous experiences of side effects and caring responsibilities.

As we would expect, there is a complex set of factors which respondents take into account in their decision-making strategies based upon a similarly wide variety of approaches to gaining knowledge about both their own condition and appropriate ways of treating it – whether or not they visit a GP or other health professional (see also 2.2).

Interviewees respond differently to information leaflets and sometimes in quite radical ways. Many set out in detail they read leaflets: particularly if they had other on-going health issues. "I am a total nightmare. If you gave me a prescription right now, first thing I would do before I even took it would be take the leaflet out and read all the way through it …"

Some acknowledged they were "quite knowledgeable" particularly in this case about factors impacting upon their child's health: feeling this awareness was a necessity.

And yet amongst some of those we interviewed there is an apparent ambivalence towards (leaflet) information, particularly if "you don't fully understand", because for one (on side effects): "…I never read them it would just worry me if I read them. I just throw them away."

It is far from clear whether this ambivalence about "knowing enough" was simply borne out of health anxiety or a genuine lack of interest: this

might need further investigation. Similarly others noted specifically they "disregard" leaflets coming through the door advertising pharmaceuticals and rely on their doctor if they need additional medication or other products. Some interviewees noted that this information can make them hesitate: "I do sometimes think that information leaflets though can send people into a bit of panic; well they can with me."

Traditional sources of information and decision making: family and friends

Respondents appeared to rely upon a complex network of 'person-based' information sources. These varied according to a range of factors, for example the extent to which they had family and friends nearby providing information on their own experiences. In some cases this was based upon a family member having (in)direct medical knowledge: a number of participants drew attention to a family member having product or relevant health-care knowledge. Often these were seen as a key source of trusted knowledge upon which decision making and behaviour (for example, consumption behaviour) was likely to be influenced.

Family (experiences) in particular seemed to be a significant influence on individual decision making, one woman stated expressly that whilst she was wary taking anti-sickness medication (during a pregnancy) after a discussion with her sister: "I felt a bit more reassured". Often participants had an inbuilt family-based cultural resistance to medicine use more generally: "...I am from a family that just don't really take drugs unless you are dying [laughter]..." Not all these sources of knowledge are necessarily seen as fail safe: "It was a friend had them and it wasn't the usual brand that I would buy, I took them and I have never felt so lousy in my life… It was horrendous". But others reported family member's negative experiences as influencing their own decision not to use particular remedies. So respondents drew attention to the observable (and different) experiences of family members. Nevertheless the experiences of family members, whilst important, were not necessarily the ultimate arbiter: "…it hasn't stopped me from taking things directly…"

Online and other research avenues

In addition some participants noted they had undertaken more active searching of information about health conditions and of potential remedies through (now conventional) searching on the internet, but also sourcing information from more 'traditional' mechanisms: medical textbooks and magazines. With differing degrees placed on these as trusted sources. "…I have got a reasonable habit of trying to understand something before I use it. I do a bit of research and look it up. You hear that many things about side effects regarding drugs … so I just want to be sure."

Professional expert advice, relationships and associated barriers

The perhaps, expected main source of information was that of medical professionals and indeed many of those we interviewed identified these individuals as a significant factor in this. But the supposition here is that these are less frequently directly encountered in comparison to friends and families. What is less clear is which of these is assigned greatest weight, given that encounters with family and friends are likely to be more deeply embedded in everyday life than those with medical professionals.

There are strong indications that individuals layer their information-seeking strategies gaining information often for the same condition from different sources both with professionals and drawing upon the experience of others. Whilst some placed all their faith in medical professionals: "I'd rather have medical guidance rather than making my own misinformed decisions..." another noting "my doctors are very good".

Proactive approach

Some individuals specified they were proactive in their engagements with medical professionals seeking information when visiting a GP: "…the first thing I want to do is I want to know the side-effects of it … I'd want to know how it works." In some cases respondents indicated they challenged GPs directly – notably when they had complex health issues and drug interactions might (negatively) impact their health: "I have actually phoned up in the past

and said 'look the leaflet is saying and I have looked it up on the internet I should not be having this because of the [pre-existing prescribed] tablets". Some respondents noted an apparently good relationship with health professionals: "... the GP went above and beyond his call of duty... I felt that he was really clear in exactly why he was upping the dosage. ... I was very impressed by that."

The relationships interviewees perceived between themselves and their doctors varied; partly this is based upon the role they chose to take. One noted that in an encounter with her doctor: "I said to him "Do I need all of these?" and he said "Yes" and that was it."

Consequently a number drew attention to the nature of the professional relationship and clearly did not want to abuse that. For example avoided visiting the GP for things they perceived were a waste of (the professional's) time. Additionally some expressed a view that (other) people should be more responsible using these services, as one noted: "...one of the things that I think is really silly is somebody has a slight cold and they're running to their doctor. Well, you know what the doctor is going to tell you... they clog up a doctor's surgery for trivial things." Similarly some recognised that, as professionals, doctors may not have answers for all complaints so for some there appears to be a resignation the doctor: "...doesn't have an answer to everything..."

Trust and professional relationships

A central element which emerges from the research is the trusting (or otherwise) relationship that interviewees had with their GP and similarly specific medicine use as a result: "I have such a high level of trust in them [doctors]..." However, some had a very negative view and experiences of the information provided by their GP: "My GP is rotten, he never explains anything, he is awful. It is just a case of you walk in, you get stuff thrown at you, you take it and you leave."

This negative element related to information provided one claiming they had been told: "Don't read that bumph…" [about side effects], whilst others identified inconsistencies in treatment particularly when a new GP had taken over (their case). Some respondents also identified themselves as lacking confidence in discussions with GPs: "...sometimes with the doctors I don't understand but I don't want to ask too many questions just in case he thinks I am illiterate or whatever. [Laughter]..."

Pharmacy / Chemist

There were also very positive impressions gained about dealing with other (medical) professionals: "I find sometimes pharmacists have a very good training and are very good with the drugs, and sometimes they have got more information on the drugs than your doctor."

Drug companies

A few participants, often with strong ethical standpoints, noted they tried to avoid products which they were aware of emanating from large pharmaceutical companies: "I would not buy from any of these companies I will do my utmost to avoid it, ... because they all torture animals..."

Whilst it did not seem to be a view expressed by a large proportion of those we engaged, there was a degree of criticism about the role which pharmaceutical company's (marketing) can play on the impact of medicine consumption. Again such negative perspectives occurred elsewhere: "...what is so galling is that the pharmaceutical companies make them for pennies, they make them for twenty pence and then they sell them to the NHS for eight pounds... these companies can charge whatever they like."

Media

Some of those we interviewed indicated that they felt bombarded by the media and related health stories – one for example felt "panicked" by "pig flu" (and other) stories. As a consequence, this individual was suspicious of the message, so didn't get vaccinated as she apparently distrusted the message.

Conclusion

To varying degrees members of the public rely upon 'authoritative' sources for information on medicine use and clearly differentiate these in their thinking and decision making. However, these are not uniform: not all respondents (dis)trust their GP for example, but neither do they rely on them for all medical needs or health-related advice.

Summary:

Participants appeared to rely upon a complex network of information sources. Nevertheless, whilst many wanted to be well informed this was not true for all respondents. How 'consumers' factor in, and weigh up, the different sources in terms of credibility and those which are most likely to lead to action is less easily determined. However, the role of the doctor (primarily GPs) clearly had a major influence, at least with respect to the use of prescription medicine.

The character of doctor-patient relationships can be described as a spectrum which we might identify as lying from authoritative to interactive. Trust and positive experiences are reported in both authoritative and interactive relationships, but distrust and negative experiences predominate in authoritative relationships.

Good and bad experiences can be associated with the level of information and the time taken by the doctor to explain details about medication; although not everybody prefers more information. People would often like to ask questions but do not always have the confidence to do so. Some people find the pharmacist easier to approach with questions.

A number of respondents reported that their proactive questions to the doctor had led to adjustments in their medication, particularly where the doctor had not been aware of all other medication they were taking, suggesting that such interaction can improve treatment outcomes.

Respondents have complex relationships with (medical) professionals. What underlies this is the sense of trust they have, whether it is with individuals directly or, more intangibly, with pharmaceutical companies (marketing). These can impact medicine consumption.

Policy pointers:

- Although price is a factor in purchasing decisions, its influence is ambiguous: a high price could make a product either more or less attractive to buy.
- As a result, price control might not necessarily be a useful driver for behaviour change with regards to OTC medicine purchasing and hence might a be a problematic 'intervention point' (though maybe for other stakeholders).
- People's OTC purchasing decisions are influenced by a complex set of factors.
- This 'diffuse information' source does not offer a single straightforward point of intervention for the reduction of OTC consumption but rather suggests a multi-pronged approach.
- Pharmacists' advice and advertising are two areas where some influence may be had.
- People's responses to Patient Information Leaflets (PILs) are varied; they are sometimes scrutinised, sometimes not read at all or not taken seriously.
- The apparent ambivalence about 'information' may need further work to establish whether it is information per se that individuals have a reluctance to receive, or whether barriers are associated with its format or context in which it is received.
- It is suggested that encouraging members of the public to engage proactively with professionals for information and advice would be beneficial to a range of outcomes, as would ensuring this information is more accessible.
- In addition given the variety of sources used to gain information and the differential levels of trust – there is a clear indication that any intervention approaches would need to build awareness of these various sources into their strategies.
- There are also clear indications that over the longer term substantial engagement with a range of stakeholder groups may generate new approaches to prescribing and acquisition of medicines.

4.3.3 Home storage

Storage practices

When we look at the evidence from participant interviews there is a general tendency towards a relaxed attitude to home medicine storage (both OTC and prescription). For example level of usage being cited as a particular consideration for deciding where to store medicines: "...it just really depends how often it's needed where it goes." Some recognised that they had "...never given it much thought" and kept medicines together to ensure "...they're always in the same place". This relaxed attitude to medicine storage sometimes produced a nonchalance: "Every so often our house gets into such a state we just kind of shove everything into bags and shove it up in the loft and out the way, basically. Not things that are used regularly; but there are things that have been prescribed, that I've decided in my wisdom not to throw out, but they've been shoved in all sorts of places."

Additionally, participant sometimes sought advice from family members, although reasons for these suggestions were not always known: "My sister, she told me it's better to keep it in the fridge. I'll have to ask her why, what's the difference?" Whilst others followed storage instructions stated on the medicines: "If it says keep it in the fridge I would put it in a fridge."

The importance of convenience was key to a few of the respondents choosing to keep medicines (both OTC and prescribed) in their kitchens. By choosing to keep them in a visible and handy place, some respondents found it easier to remember to take their medicine: "...because I take them after my breakfast you see, so that's why I have them in the kitchen so I'm not taking them on an empty stomach."

Storage practice vigilance

Most participants (both with and without children) appeared to have a clear understanding of the potential dangers of leaving medicines out and within reach of children. Those with younger family members often cited them as a key consideration in ensuring that their medication is clearly out of sight and "not lying about". Seeking "a nice safe locked environment" for medicines was considered paramount. Learning from the mistake of others to create better storage practices of their own was emphasised by one participant whose own sister had had medicine stolen through an open window: "...she used to keep her drugs in the kitchen on her worktop and it was near a window and the people in that area were stealing. ... it just stuck in my head."

Whilst few of the respondents made any clear distinction between where they kept OTC and prescribed medication, in contrast, a common sentiment was a priority to keep medicines in convenient locations, either "all together, one big mess", or "a packet here and a packet there".

There was a common understanding across participants that actively carrying medicines out and about with them was "really not good" yet, it would appear that this is a regular practice with respondents purchasing OTC products and "...then just throwing them in my bag". This need was seen as a pre-emptive measure by some, to save from having to purchase OTC medication for symptoms regularly experienced: "...because nine times out of ten I end up with a headache..."

However, one respondent emphasised their wariness over taking medication outside the house, more specifically, whilst on holiday. They reported a concern over people watching them and, potentially, trying to steal the medication.

Summary:

Storage behaviour appears to be driven by two main considerations: convenience and safety. Particular safety concerns are children having access to medication and theft of medication. Behaviours are sometimes also influenced by friends or family and by specific storage instructions (for example on leaflet or packaging). There is some indication that by some, disposal of medicines tends to be done by an occasional 'clear out' rather than by returning individual products when finishing a treatment.

Policy pointers:

- As returning medicines to the pharmacy may increase the time medicines are stored at home, suggestions for safe storage of waste medicines may help to address any concerns the public may have.
- There is existing goodwill around the safe and secure storage of medicines, which can be built upon.
- There might be wider, more strategic implications for prescribing policies and patterns resulting.

4.3.4 Disposal behaviours

Flushers & crushers: practices of disposal

One attitude across participants was that, as many tablets "melt away" and dissolve in water, it was safe to flush or pour unused medication (tablets and liquids) away and was a common practice amongst a number of respondents: "Well, I feel that I can dispose of the liquid myself quite happily and efficiently. It's well away, it's down the sink and the bottle is rinsed. Nobody is going to drink it or do anything." The issue of 'safety' resulted in one respondent advising others against "hammering" their unused tablets in favour of seeking other disposal methods, such as putting them down the toilet. Unlike bins, where people could access them and self-harm, flushing or pouring provided some respondents with a sense that this was a safer alternative.

Reduction in harm perceptions

A key consideration against flushing or pouring medication, for a limited number of respondents, was its potential impact on the water system and its wildlife: "I read somewhere, I think it might be true, like, if you take a pill, and then go to the toilet and you pee, then like that hormones they get into the sea, and fish will also be under these hormones, so the fish population will be dying."

Yet, despite these concerns, there was little specific or concrete knowledge on the explicit implications on how these medications may result in negative (environmental or other) consequences. Respondents referred to "horror stories" and the potential future impacts for humans and future generations. Particular reference was made to contraceptive pills and "female hormones to become into the water system". Not only were environmental consequences stipulated but also the potential for human "poisoning" through affected fish stocks and "creating defects".

Uncertainty over the exact source of these ideas and views did lead some to consider that they may be overreacting: "...it is a wee bit extreme."

Summary:

- As with storage, safety and convenience are key considerations for disposal.
- Because safety considerations relate primarily to access by other persons, disposal via the toilet or sink is perceived by some to be safer than disposal in the bin.
- People are prepared to go to considerable length to ensure medicines are disposed of 'safely'.
- In particular liquid medicines are disposed of via the sewer.
- Some people were aware, although not in detail, of environmental issues around disposal via the sewer, including the fact that residues may end up in drinking water, and would actively avoid disposal via the sewer.

Policy pointers:

- With a clear message in an effective format, it may well be possible to 'redirect' people's well-intended behaviour towards returning pharmaceuticals to the pharmacy and away from disposal via the sewer.
- disposal information in the PIL may not be read and alternative information sources may need to be provided.

Take back – pharmacy

A common practice of disposal was returning unused medication to the pharmacy. There was a general attitude that, due to more specialised knowledge, they would be "better disposing of it than us".

A distinction between what forms of medication should be taken back to the pharmacy was noted. Some respondents stipulated that if "it's prescribed I would rather hand it back into the chemist". Furthermore, it was apparent among respondents that, whilst tablets should go back to pharmacies, there was less certainty over creams and whether they could be recycled. An alternative reason for returning medication to the pharmacy was the need to get something replaced when it failed to solve the symptoms: "The reason you're taking it back is because you've had a reaction to it and you'll get something else." Furthermore, some interviewees referred to "double dosing" to "prove", to the pharmacist professional, something is not working for them and to ensure other medication is prescribed to them upon returning their unused medication.

Several people suggested that convenience was a key element in their deliberations, drawing parallels to municipal recycling. This is also hinted at by one particular interviewee: "I think if I had just one left in [the] packet I am not going to go to the pharmacy for just one but if I had a series of boxes left untouched then I would take them back".

Not all participants knew unused medicines could be taken back to the pharmacy. Some participants appeared frustrated with the lack of clarity on disposal arrangements one tried to return a box of used syringes to the doctors and the chemist in vain, before contacting the District Nurse and getting a positive response. Asked how she felt about having to try various professionals, she said: "…It was when I could not get anyone to take them; I was saying I cannot put them in the bin."

Participants that did know they might take medicines back to the pharmacy did not always understand why they were being asked to do so. One participant thought only medicines that were still within their expiry date should be returned, as he assumed they were collected primarily to be dispensed to other patients. Consequently, he felt there was no point in returning out of date medicines. Several participants felt it was wasteful that returned unused medicines are not always dispensed to others and felt savings could and should be made by doing so.

Recognition of partial knowledge – 'good disposal practices'

The practice of disposing medication in the bin was frowned upon by many of the respondents who felt that an animal, other people or children could have easy access to them, with potentially disastrous consequences. As such, some respondents referred to dissolving and flushing medication as being more preferable.

To deter "bin-rakers", one respondent claimed she ensured non-medical items were put in a pharmacy bag whilst medication was stashed in another.

The role of advice from friends, family and experts was clearly demonstrated with respondents referring to others as being more knowledgeable on proper disposal of medication than themselves.

Conclusion

It is apparent that a major gap in people's knowledge relates to the appropriate disposal of medicines. Individuals were clearly, in many cases, investing much time and sometimes effort into ensuring disposal was done safely within the household. In some cases there was shock when it was revealed this was against conventional advice.

Summary:

- Not all participants knew unused medicines could be taken back to the pharmacy.
- Several had heard about the take-back scheme from friends and family.
- Some participants had had (practical) difficulties returning medicines to the pharmacy and experiences with the take-back scheme differed.
- Many participants did know why they were being asked to return medicines to the pharmacy and thought the primary reason was to enable reuse of returned medication, which sometimes led to sub-optimal disposal behaviour or negative attitudes.

Policy pointers:

- Clear, consistent information on the practice and rationale of disposal facilities may encourage optimised disposal behaviour.
- Peer education may be an effective way to encourage behaviour change around disposal.
- Given the considerable willingness to 'do the right thing' amongst participants, raising awareness may be 'low hanging fruit' in terms of achieving a reduction of pharmaceuticals in the environment.

4.3.5 Disposal: perceived responsibilities, policy and practice solutions

Respondents noted that possibly the GP should provide some explicit instructions or facility for the disposal of medication. The role of the chemist was also highlighted as a solution, with one respondent expressing they felt: "that the Chemist has got some kind of plan to safely dispose of pills that nobody in any way could get their hands on". Some highlighted that there had been some confusion over where to return disused medication and they "could not get anyone to take them".

When asked to consider how best to improve medication disposal, one key recommendation emerged; the provision of a secure bin at the pharmacy. However, it was emphasised that this must be "in a certified area" to ensure no-one could steal from it: "I suppose some crazy person is going to steal medication if it was just lying out at the front". Furthermore, this system would not use up staff time unnecessarily, a concern raised by one respondent.

The current lack of, and need for, publicity, either on medication disposal itself or through a media campaign was raised by some respondents. Similarly, the need for more awareness of what 'recycling' medication actually means or entails was highlighted. One respondent suggested a possible "out-of-date-drug amnesty" solution, similar to a previously held "knife amnesty" by the police. A further prospective solution was the introduction of financial incentives for the return of unused medication, with vouchers for future purchases of medication being issued.

Summary:

- There was a general belief in the need to keep collected medicines in a secure bin or area.
- Some participants indicated that they would prefer a more anonymous disposal facility, such as a bin in the surgery or pharmacy.
- The required interaction with the pharmacist when returning medicine can be a barrier to use of the facility; it can cause embarrassment, fear of criticism (for not completing the course of medicine) or concerns over wasting pharmacist's time.
- However, some participants appreciated the opportunity of a conversation with the pharmacist when returning medicines.

Policy pointers:

- Further research is suggested to optimise the practical operation of pharmaceutical take-back schemes.

4.3.6 Awareness of environmental effects

A limited number of respondents, without prompting in interviews, drew attention to wider environmental impacts: "I'm responsible for the planet I live on as well to a certain extent. And if I thought I was doing something that was detrimental to my environment, I would personally want to look at that." One respondent had heard about hormones posing a risk and changed her behaviour for other medicines. She explained why she didn't put a particular medicine down the drain: "I don't know. I just think that if everyone is putting them into a water system, is it going to affect things somehow? Is it going to get back to people? Is it going to get into their drinking water if it's not cleaned. ... Wasn't it women disposing of contraceptive pill or something like that, and ... hormone levels in the water ... creating defects in young males, the male children. Someone had either told me about that and I had read it years ago. I just don't like the thought of putting it down the drains". And on one occasion concern about wildlife: "And I am now thinking to myself should I, is there a wee fox that is going to come along and OD on it."

4.3.7 Day-to-day cultural practices governing views about the value of medicines and the potential for (behaviour) change

There was substantial evidence that 'everyday' approaches (myths?) to healing and health were prevalent and had a significant impact on many people's behaviours.

Lifestyle and behaviour: the desire for change

There was a palpable sense amongst some members of the population that they wanted different (often, long-term) solutions, including taking greater personal control and responsibility or options with regard to their own medicinal use: "I don't think that medication is always the solution. I know that it can be and often it is and instead of taking [named medication] for myself, I would like to eat healthier, I would like to have three big meals, a nice sirloin steak every day and I would like to run 10 miles every day before I go to work." Implying, one suspects, that their own lives had become overly dependent upon the medication but in this same person's case they acknowledged that: "...in all likelihood, I am not going to do that …".

In other cases individuals were actively seeking to change their medicinal use, for example avoiding antibiotics because: "a natural immunity" is more effective. For others the associated concern was with their own over-medication or dependence (for example with respect to anxiety medication): "…if my intention is to come off them then I have to try and cope." Another noted: "…over recent years I have been trying to stay away from taking painkillers as an initial reaction to any kind of pain… if I get headaches I will try and modify my diet first…"

Others were actively seeking alternative approaches for example: "… I do yoga now" (to take the pain away). One interviewee, over recent years, had decided "to get healthy and sort myself out." In some cases individuals appear to pay attention to signals from their own body, for example one interviewee noted that if they had a mild headache developing it was probably because they had not been drinking enough water: had become dehydrated, so in the first instance they would drink water. But at the same time the person acknowledged also that if it were severe then they would medicate it (with paracetamol).

Wider medicine use – prevailing culture in Scotland

At the end of each interview we asked interviewees to ponder as a society we take too many medicines no one demurred from this. Some expressed strong views as to how society should / might respond to a perceived overuse of medicines: "…I think that as a society I think kids need to be weaned off of going to the doctors and getting drugs for everything; and get more healthy things…" And another argued: "I think people are becoming a wee bit too sort of reliant and soft and wanting mollycoddled all the time by the NHS."

Conclusion

Members of the public volunteered a wide range of perspectives indicating their view that control and responsibility as well as a desire to change health behaviours was an important issue. For some it was clearly a predominant concern, in as much as they had clearly put in considerable thought and in some cases physical energy into seeking to change towards more healthy behaviours, as they saw them. But most of these indicated it was difficult and in some cases explicitly noted they needed help with this.

Summary:

A number of people expressed a certain faith in 'allowing the body to heal', preferred natural remedies to 'chemicals' or used natural remedies as complementary to pharmaceutical products. There was attention for positive lifestyle choices such as diet and exercise as a way to reduce medicine use and a general belief that individuals can take greater levels of control and responsibility over their health.

Policy pointers:

- It may be worth exploring the extent to which people seek reassurance (that they will heal naturally), rather than medication, from their doctors and other professionals.
- The promotion of positive lifestyle choices such as diet and exercise are recognised as beneficial both as preventative and as curative health interventions; barriers to implementing these might be explored and addressed.
- Overall we can conclude that there is considerable gratitude for the access that individuals have to medicines through all the different channels but equally a profoundly held belief that there is an overconsumption.
- The indication is that individuals would appreciate more (easily accessible) information about alternatives but also more widely about appropriate related behaviours for example disposal.

4.3.8 Solutions – evidence from workshops – public perceptions of responsibilities

As a second phase of the qualitative study we undertook a series of workshops with those who had participated in interviews and present this analysis here as a separate but linked element.

A range of themes relating to pharmaceuticals in the water were explored during the workshops: storage, consumption and disposal of medicines; notions of 'risk' and 'safety' relating to consumption and disposal of selected medicines, water quality, and attitudes to (environmental) responsibility and achieving behaviour change. The primary aim of these events was to explore what might be seen as realistic solutions for example towards changing individual's consuming behaviours and disposal habits.

Thoughts on the reduction of pharmaceuticals in the environment focused on a number of distinct areas: things 'people' (i.e. consumers / patients) could do; things specific stakeholder groups (doctors, pharmacists, pharmaceutical companies) could do; improving disposal facilities and suggestions for education and awareness raising.

The general public

There was a general preparedness to change disposal behaviour, although informants perceive laziness and a lack of time as barriers. One participant commented that supermarkets have taken people away from pharmacies their opportunity for gaining advice. In two workshops, the prescription of medicines was seen as a two-way process, where although doctors and pharmacists are the 'experts', people should ask more questions about the medicines they are prescribed, such as whether medication was likely to be long term or what would happen if a medicine is not taken, but one individual identified it as quite clear cut: "if people need a prescription, they need a prescription".

Stakeholders

Stakeholder groups identified as having a role were doctors, pharmacists, pharmaceutical companies and local authorities.

The ease with which repeat prescriptions, which are free in Scotland, are available is seen by some as unnecessary and something that should be addressed in prescribing patterns, with one reporting that elderly relatives had large quantities of medicines. One thought doctors may prescribe medicine when not required because they feel that is what people expect.

The provision of convenient disposal facilities was suggested numerous times, with suggestions for 'special bins' in the doctor's surgery or by provision of bins for kerbside collection with recycling: "in case people cannot always make it back to the pharmacy". Although, safety concerns are voiced in relation to the latter. The comparison with recycling behaviour was encouraged during the workshop and several people considered that if it had been possible to engender a behaviour change for general waste disposal, it would also be possible to do so for medicinal waste; provided that people were well informed and that access to facilities was easy. Some had experience of being fined or otherwise coerced into correct recycling behaviour; one participant thought this had been an effective way to change her behaviour but participants in another workshop did not feel punitive measures were a good driver of behaviour change.

Information and publicity

Publicity, awareness and information were perceived as important. One suggested "graphic demonstrations" of what pharmaceuticals do when they get in the water. Some remarked the medicine leaflet (PIL) is too long and not an effective place to inform on disposal. The pharmacy and the doctor's surgery were seen as good places to provide information, for example using posters, flyers or leaflets.

Use of a 'peer group' to raise awareness and education in school was also seen as potential mechanism. It was felt that Local Government could play a more active role in informing the public and that the message should be tied in with disposal messages for other (recycling) materials.

Conclusion

Members of the public provided real insight into an agenda which many had not thought about and it is clear there was considerable goodwill to 'do the right thing'. Whilst many, in their own lives, were seeking to reduce their own medicinal use or were receptive to the idea it is equally apparent this faces several challenges, not least that much of the problem (regarding consumption) is seen to lie with 'other people'. Nevertheless when individuals were asked to consider appropriate disposal mechanisms, many were keen to understand the appropriate i.e. 'safest' way to do this. In policy terms this gives a firm building block on which to build responses and potential interventions.

Policy pointers:

- People are familiar with the concept of correct and incorrect disposal (for example, through experience with recycling collections).
- People are in general prepared to separate their waste and dispose of it correctly, particularly so when considering safety (for people) is an issue.
- However, there are many misconceptions about
  - what constitutes 'safe' disposal of medicine.
  - what medicines are accepted by pharmacists.
  - why medicines are collected by pharmacists (and this affects compliance) which might need to be addressed if behaviour is to be optimised or habits changed.
- People have little or no understanding on the cost that would be involved in advanced wastewater treatment and may be more prepared to change disposal behaviour if they were.
- Information, education and publicity would be welcomed, both on disposal advice and on the wider issue of pharmaceuticals in the environment.
- The 'waste disposal' message on pharmaceuticals may be usefully included in local authority recycling information.
- There is scope to improve disposal facilities as there are still several perceived or actual barriers.
- People feel a range of stakeholders could contribute to the reduction of pharmaceutical consumption and are also prepared to accept that they themselves have a role to play.

4.4 France

4.4.1 Introduction and method

The study concerned perceptions held by a variety of actors, of water issues and cultural, social or imaginative representations relating to medicinal residues and their presence in waters involved in the life cycle of medicine.

The study centered in particular on current practices in every stage of the medicine cycle and on the actual or symbolic link between these various actors on one hand, the medicine and on the other hand the environment, by assuming that the perception of the medicinal residues in the water is connected to the social, cultural and symbolic representation of the medicine as well as to the practices which ensue from it.

The geographical scope of the study was the Limoges Métropole conurbation, which has approximately 212,000 inhabitants (http://www.agglo-limoges.fr/). The Limousin region, within which Limoges Métropole lies, ranks first in terms of regional performance for inhabitants' recycling of medicine (Cyclamed, 2013). Limousin is also one of the regions where an experiment on the dispensation of antibiotics was set up over a period of 3 years. In January, 2014 the city of Limoges launched a 'City Health Citizen' charter, which aims at developing 'actions santé' (Health Share) around water quality.

In France, in 2013, 2,800 different active substances, corresponding to 11,000 formulations, were available on the French market. The total amount of the sales of medicine has dropped slightly since 2012. Medicine sales in France are worth 26.8 billion euros. On average, a Frenchman/woman consumes 48 boxes of medicine a year, equivalent to 3.1 billion

boxes in total. The most commonly used active substance in communities is paracetamol, whereas in hospitals, the most commonly used active substance is the bevacizumab, an antineoplast.

In 2011, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) published the results of a national analytical campaign of 76 pharmaceutical substances in water. 30 substances were detected at least once in natural water, of which 16 were found at concentrations above the limit of quantification (LOQ). The Ministries in charge of Health and Ecology initiated a national plan on medicinal residues (PNRM) to estimate potential human and ecotoxicological risk associated with the presence of these substances, and to reduce pharmaceuticals in the natural water. (http://www.sante.gouv.fr/plan-national-sur-les-residus-de-medicaments-dans-les-eaux-pnrm-2010-2015.html) ** Assuming that the entire chain of actors plays a part in the problem of medicinal residues in waters and that any 'levers of action' will relate to perceptions of actors in each category, the typology of social population used for this study was as follows:

- Producers: pharmaceutical companies, pharmaceutical sales medical representatives
- Distributing: wholesalers-distributors,
- Dispensers: pharmacists,
- Prescribing doctor: doctors, specialists,
- Administrators: nurses, midwives,
- Regulators: French National Agency for Water and Aquatic Environments-Onema , Regional Health Agency – ARS, Regional health insurance, mutual insurance company,
- Professionals of the water industry and management,
- Regulators
- Users: patients, consumers,
- Whistleblowers: associations, Non-Governmental Organisations (NGO)
- Scientific community

4.4.2 Environmental awareness

4.4.2.1 Perception of the problem of pharmaceuticals in water: general public, doctors and pharmacists

The majority of respondents across all categories believed that pharmaceuticals have a strong impact on flora and fauna. Pharmacists however seemed more divided, as 38% considered that medicine has a low impact. In all respondent categories, the disruption of reproduction and the feminization of male fish were the most important perceived impacts, likely due to the media coverage. Pesticides and endocrine disruptors are substances that were of great concern for all groups of respondents (doctors, pharmacists, residents), about 30% for pesticides and about 20% for endocrine disruptors. Subsequent in order of concern were nitrates and drugs (about 19% for nitrates and 18% for drugs). However, for 22% of doctors, detergents were more worrying than drugs and nitrates. Of less concern were cosmetics. For doctors and residents, the highest priority substance group was pesticides, while for pharmacists, it was nitrates. Drugs were placed third.

Most (> 80% responding) people of Limoges Metropolis had heard of drug residues in water from the media (television, national newspapers, radio). 57% of pharmacists considered anti-depressants to be the most commonly found drugs in water while 77% of doctors thought it was antibiotics. Residents were more divided between the different categories of drugs than health professionals: 25% of residents believed that analgesics are the drugs most commonly found or found in the highest quantities in waters, 23% thought it was antibiotics and 20% antidepressants.

Most respondents in all three categories considered that drugs arrive in waters via toilets, then via the waste water treatment plant; less thought hospitals were the main source (Fig 4.1).

* In 2015, this PNRM will be integrated into the micro-pollutants plan. The National Plan for health and Environment 3 (PNSE3) (2015-2019) plans to prioritize actions to better understand emissions, and in particular to improve knowledge on toxicity of pharmaceutical residues.

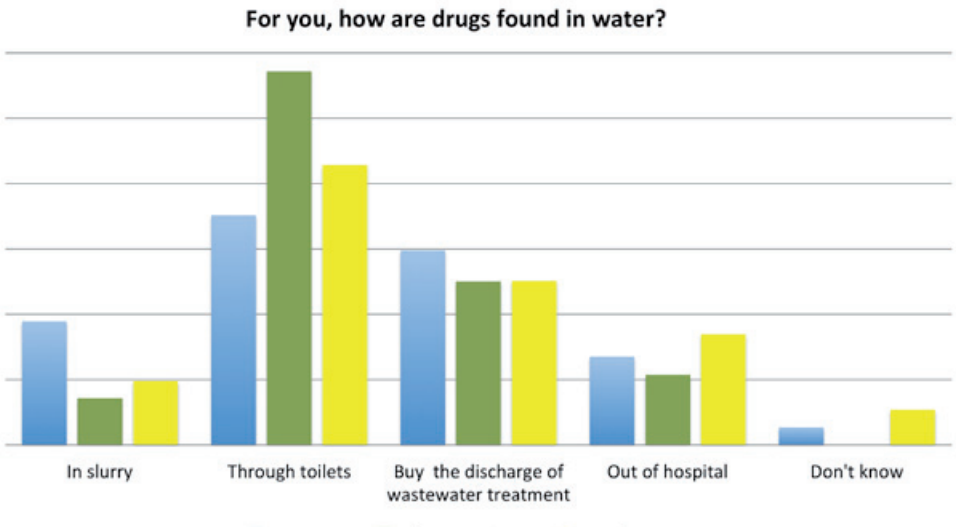


Figure 4.1: For you, how are drugs found in water?

4.4.2.2 Approaches to dealing with the problem of pharmaceuticals in water

During workshops, 10 levers to reduce pollution by drugs were identified and discussed: training and research; improved water treatment; recovery methods; prescribing practices; environmental awareness; communication; new consumption practices but also legislation and the development of mediation institutions (Fig. 4.2).

Training healthcare professionals, including prescribers and dispensers, was often mentioned in individual interviews and workshop discussions. The lack of modules for environmental risk was emphasized as was the lack of knowledge on the subject, including amongst doctors.

The link between health professionals' training and pharmaceutical industries was mentioned as a barrier to training on environmental risk. Most doctors would find specific training on environmental health useful: 71% of doctors thought it would be essential or useful, a further 21% would find it somewhat useful whilst only 16% thought it would be of little use. 87% of doctors who responded were not trained on complementary and alternative medicine, but 54% would be willing to undergo training. 28% of pharmacists had received training on the environmental impact of drugs, likely in the context of marketing authorization applications (MAA).

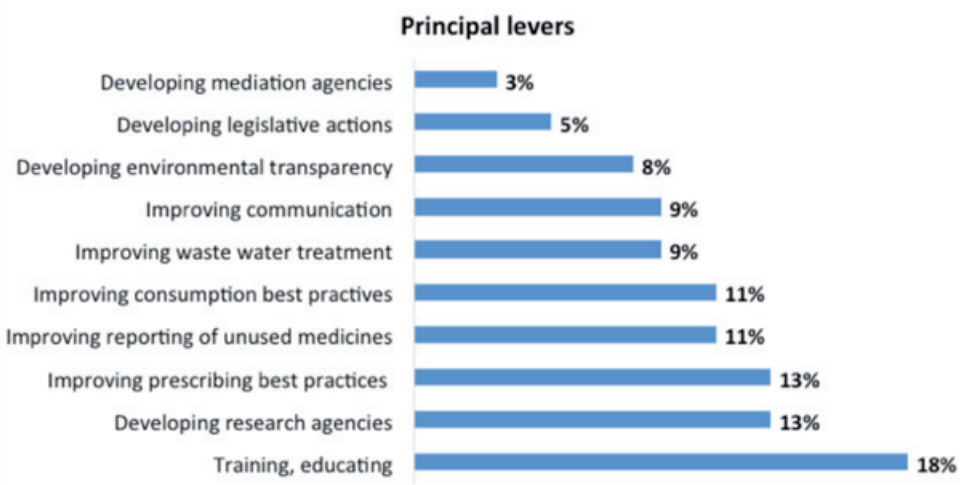


Figure 4.2: Principal levers

Policy pointers:

- Doctors would find training on environmental effects useful.
- Doctors would also be prepared to receive training on complementary and alternative medicine.
- The link between pharmaceutical industries and health professionals' training should be scrutinised for its effect on prescription volume.

Professionals highlighted people's lack of knowledge on drugs and the water cycle:

"I think a large majority of people imagine [that] when they take a drug, the drug remains in the body. It acts, it does what it has to do but it remains in the body. They do not think that the rest can leave and enter the environment with their urine or excreta via wastewater." Mr D., Water Professional.

However, residents felt rather well informed (54%), or informed (21%).

4.4.2.3 Communication, information and education on environmental issues

Communication about medications in waters can be unclear and the discourse can lead to misinterpretation of the message, including a risk of rejection of medicine use. The question can cause anxiety if information is incomplete or overly brief.

"It is especially the media treatment of this information,… can disrupt many people who no longer understand what is true from what is not. Sometimes, we offer excessive honesty, we want to be transparent, we see that transparency can lead to fear but sometimes it is better not to communicate." Mrs T Health regional Agency

4.4.2.4 Research need

Several research dimensions are relevant: health; new technologies for water treatment; knowledge of aquatic environments and drugs. Links between environment and health and multidisciplinary research are important elements in successful research and for the understanding of these complex mechanisms. Health and environment professionals mentioned research development as essential to reducing drug residues in water, because in order to act, we must understand the issues. A view was expressed that medical research must progress the knowledge about the impacts of active substances in the human body, particularly drug interactions. Moreover, the residence time of drug substances in the human body remains to be explored.

"Asking the question whether a compound has an action on a location within the body and what are the interactions with drugs. Beyond three medicines, this becomes experiment. The doctor shouldn't assume without knowing." Expert ANSES

The development of antibiotic resistance was also seen as very worrying and risk analysis methods are not yet applicable.

Policy pointers:

- There is strong support for further research, and in particular interdisciplinary research, amongst both health and environmental professionals.

4.4.3 Issues around consumption

4.4.3.1 Consumption

In the Limoges metropolis, 59% of respondents said they did not use long-term drug treatments. The most common long-term treatment was the contraceptive; for 60%. 11% identified treatment as being monitored for cardiovascular problems and 10% received treatment for thyroid. Of the 136 respondents, 79% are women and 70% of them claim to use a contraceptive pill. Treatments for thyroid were most commonly received by women. 5% reported never taking medication, 27% at least several times a month and 36% daily. Of the latter, 25% used one drug daily, whilst 8% of respondents took more than 4 drugs per day. Respondents between the ages of 18 and 29 years consumed medication least frequently and those over 70 most frequently. Long-term treatments were seen as necessary for a number of conditions (for example hypertension, diabetes): without this treatment, "life would be shorter." The drug was then seen as a benefit and its effectiveness is highlighted: "If we want to live longer but healthier [lives], it will necessarily help…" (Mr S., Pharmacist). This raises the question of dosage that is central to the design of improved drug practice in long-term treatment

"All that is chronobiology, and needs to be considered in drugs [use] because it individualizes medication. We have different strengths. Between human beings, between individuals, there are big differences." Ms. Y. ARS.

And the dosage also means an interrogation on the packaging:

"There are aberrations. [For example] There are box packagings designed for three months because it is cheaper. 3 months, 87 tablets because it is 3 times 28, but you have other laboratories where three months is 90 tablets." M. R. Doctor.

Policy pointers:

- There is some interest in individualising drug treatments, which could lead to a reduction of medicine used whilst optimising treatment outcomes.
- The size of packaging can deliver cost savings but may lead to increased wastage and might be worthy of review.

4.4.3.2 Patient-doctor interactions and adherence to treatment

Regarding prescription practice, 30% of respondents reported visiting their doctor at least once a year and 28% every 2-3 months. 45% of doctors agreed to prescribe certain drugs at the request of patients from time to time, often 39% and 11% regularly. Only 3% of patients asked their doctor to prescribe drugs and more than 70% never or rarely asked them.

Regarding medication adherence, 61% of patients said they always followed their treatment, 30% usually and 3% rarely or never. More women responded that they always followed the dosage than men (64% and 56% respectively). 24% said they always read the patient leaflet, 29% usually and 26% occasionally. On the other hand, 6% note they never read it.

Policy pointers:

- Prescribing behaviour responds at time to patients wishes.
- There is considerable scope for improving medicine-use adherence.
- The patient leaflet is often not read by patients and may therefore be of limited use for the dissemination of environmental information.

[1] Chronobiology is a field of biology that examines periodic (cyclic) phenomena in living organisms and their adaptation to solar- and lunar-related rhythms

4.4.3.3 Preparedness to change consumption behaviour

When asked about alternatives to prescription, 35% of respondents said they go to a doctor practicing alternative medicine, most commonly osteopaths and homeopaths. Meanwhile, 55% of respondents were willing to accept advice without medication for a benign disease, provided an alternative solution was proposed.

Policy pointers:

- There is considerable acceptance of non-medicine treatments for minor illnesses.

Compared to the Netherlands, where consumption and prescriptions are the lowest in Europe, in France there is a logic of "immediate repair" (providing immediate care) through medicines among practitioners (with the tacit agreement of the patients). In addition, the drug remains the central tool and the prescription meets other needs. It is suggested that medicine validates professional legitimacy: it is material proof of the physician's ability to diagnose and to "find" a cure. (VEGA Anne, 2012)

This special relationship with the doctor is important in order to understand prescribing practices and resulting consumption.

4.4.3.4 Advice and information on medicine

Pharmacists appear to play a critical role in advising and informing on medication. Pharmacists have a facilitating role between users and medicines, but also between doctors and users. Furthermore, they have a role of vigilance in iatrogenic risk (drug interactions), and are therefore in contact with physicians, patients and pharmaceutical industries. For most patients / consumers, both pharmacists and doctors inform them about self-medication. 65% of people told us they sought advice from their pharmacist on self-medication and for 64% of interviewed pharmacists they noted they always indicated the dosage of drugs. And whilst 66% of respondents did not discuss prescribed drugs with their doctor, more than 60% talked to their pharmacist.

Policy pointers:

- Pharmacists may play an important role in informing people but are apparently less aware of environmental effects than residents.

4.4.4 Storage and disposal

For dealing with unused and expired drugs, behaviour was diverse: most people said they keep them (39% most often, 24% always). They also returned them to the pharmacist (still 29%) and most (93%) never throw the leftovers in sinks or toilets. (Fig. 4.3)

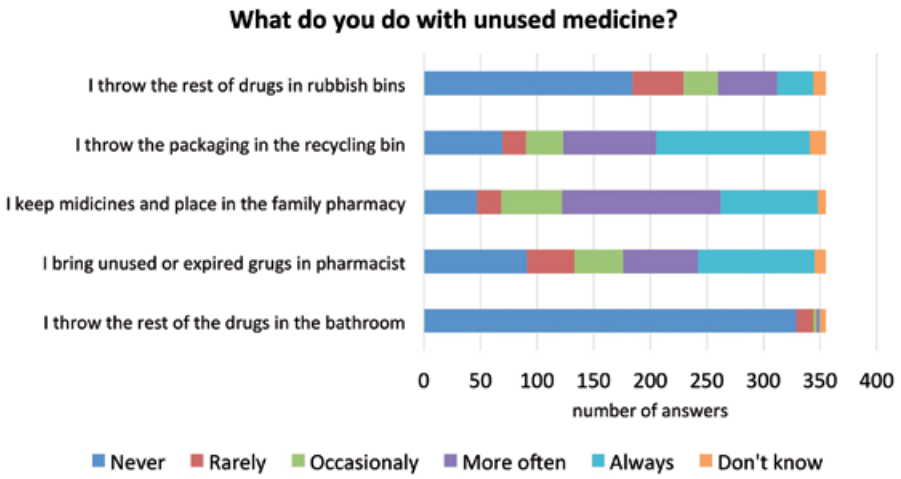


Figure 4.3: What do you do with unused medicines?

Almost 52% of respondents had between 1 and 9 boxes of drugs in their medicine cabinets and 23% between 10 and 29. One in twenty had over 41 drugs. Just over half (52%) of respondents did not know 'Cyclamed', the French system of collecting unused medication. This was primarily the case amongst the age class 18-29 years, on the other hand, most women were aware of the facility (66%):

"There was a lack of communication on the subject. The French do not see what the point is, why it is very important to destroy these drugs. There is a lack of communication about it [and]; it is mind-boggling. This is an inconsistency. Therefore, the role and purpose of Cyclamed in my opinion should be revised. Then, the communication should be structured." Mr R., CD2S

4.4.5 Rationalising prescribing

For 22% of physicians, drug treatment in health facilities could be improved by streamlining prescription. For 20%, the collection of unused drugs would be a solution and according to 18% control over drug taking would improve drug treatment (Fig. 4.4)

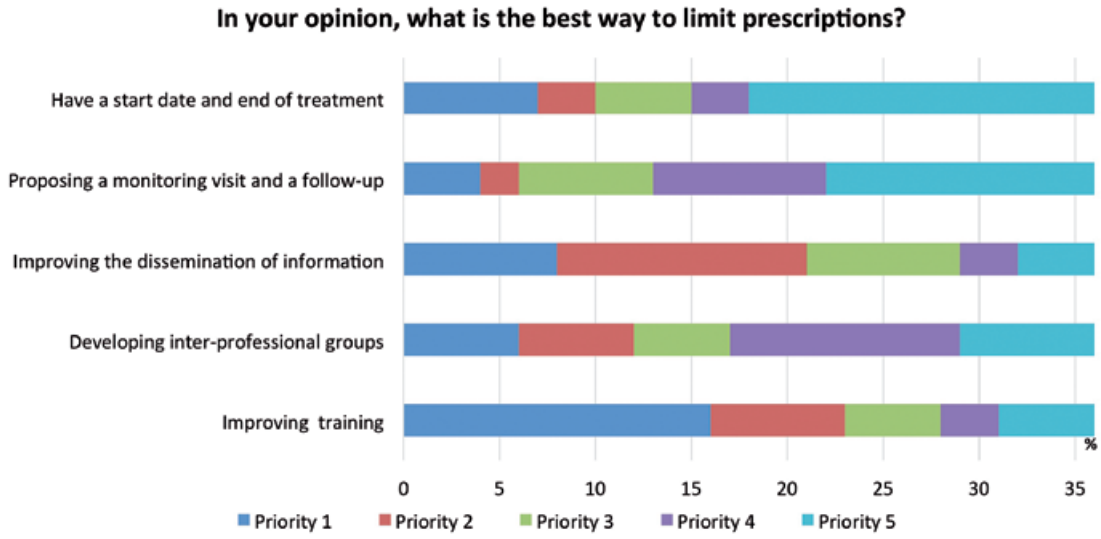


Figure 4.4: In your opinion, what is the best way to limit prescriptions?

Different scenarios to reduce medication were proposed and prioritised: an appointment at the start and at end of the treatment; control and follow-up visits; information and training; and inter-professional group establishment.

"[The doctor] is there to deal with a problem in a given part of our body, [that's] our function. The medication cannot be something that tales over our lives." Mr Z, Project Manager Sustainable Development.

4.4.6 Towards solutions

4.4.6.1 Strengthening the water treatment

16% of residents saw a reduction of the number of drugs prescribed as the most effective solution to reduce pharmaceuticals; 15% thought collecting unused medicine would be effective and 15% would reduce consumption. There was less support for the creation of an environmental tax (Fig. 4.5).

"There is the question of an environmental tax. An environmental tax is not punitive. It is giving a real cost to a product or for the producer to absorb the true cost of the product." Mr. H., Environmental Defence Association.

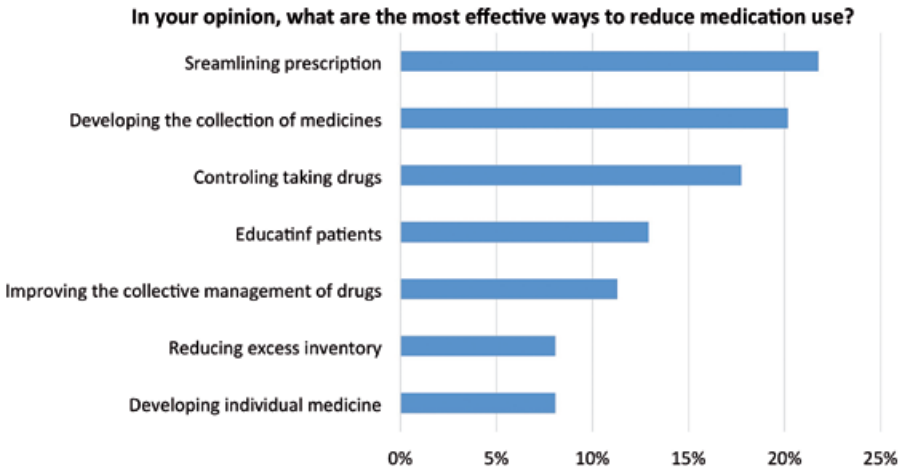


Figure 4.5: In your opinion, what are the most effective ways to reduce medication use?

Among the various methods for reducing medication in water, improving water treatment was supported least, with only 9% of respondents thinking that it was an effective solution. Treatment was seen as a necessary solution but must occur after preventive actions. Concerning the cost of any water treatment, 84% of people felt they were not prepared to accept an increase in the price of water.

"On the final treatment of water, our position is that we have to control, as best as possible, what waste is generated. If possible then, to reduce overall consumption, it is there where least effort is needed: hence treat them as close as possible to source" Mr B, water manager.

"Potentially, it would be possible to treat many more drug residues until about 96.97% has disappeared. 98% but with huge costs since, as a first approach, that was three years ago, it was estimated investment of € 12 million [would be necessary] to treat drug residues and general organic micropollutants." Mr D., water professional.

The in-situ treatment of hospitals' effluent is not seen as a good solution because it is partial and because, with the increase of ambulatory care it would be less effective; the development of ambulatory care leads to proposed solutions outside the traditional frameworks of treatment.

"Treatment at the hospital is useless because drug consumption is now [undertaken at] home mostly. It must be treated at the wastewater treatment plant." Mr Z., responsible for Sustainable Development Mission.

Policy pointers:

- Prescribing, consumption and disposal behaviours are all seen as useful levers for the reduction of pharmaceuticals in water.
- There is little support for measures that would incur a cost to residents, such as an environment tax or additional water charges.

[2] PBTs are a unique classification of chemicals that have and will continue to impact human health and the environment worldwide. Environmentally Classified Pharmaceuticals (2012), Stockolm County Council.

4.4.6.2 Environmental Awareness

The Persistence–Bioaccumulation-Toxicity (PBT) index seems an interesting solution but was known only to 6% of the pharmacists and 11% of the doctors. However,

"[As an organisation] We decided, because [government] did not move it [PBT] forward for 7 years, to fund a smartphone application. The doctor who types the name of a medicine will [now] have the drug PBT index." Mr S., CD2S Association for sustainable development in heath sector.

A PBT guide is also available on the website of the URPS of the Languedoc Roussillon region (France) and a legislative proposal to establish an index measuring the persistence, bioaccumulation and toxicity of drug residues in surface water, was filed in July 2013 in the National Assembly. 33% of people wanted the environmental impact of a drug to be noted on the box and 19% on the leaflet.

4.4.6.3 Legislation

Legislation is an important lever to address the issue of drug residues, through monitoring and by the implementation of regulatory tools, such as a programme of measures.

"…Of course it must be changed through the legislation. We need rules and more control. If people were taxed on drugs they throw, they would act differently." Mr S., CD2S Association for sustainable development in heath sector.

Summary: following measures supported by actors in the medicinal product chain:

Producers	Develop Green Chemistry PDT index environmental indicator Logo „green" Change conditioning
Distributors Dispensers	Develop recycling process Change conditioning Individualize dispensation
Pharmacist	Develop advice Share information Develop recovery of drugs
Prescribers	Develop personalized support Information and awareness campaign De-pay the most polluting drugs Create a tax on the most polluting drugs Educate on health
Regulator	Develop personalized support Information and awareness campaign De-pay the most polluting drugs Create a tax on the most polluting drugs Educate on health
Professional (water)	Monitor drug residues Treat sewage and develop appropriate technologies Better inform the public
users	Awareness of a non-drug management Tip Sheet training Limit consumption Aware of the impact Develop the concept of medicine „in case" alternative solutions
Scientists	Applicable analytical methods Knowledge of cocktail effects Pharmaceuticals in the environment Bioaccumulation More respectful drugs New methods of treatment communicate
Legislator	Measure and monitor Clear regulatory framework Severely restricted authorization of market conditions

4.5 Germany – evaluating interventions

A case study in Dülmen focused both on capturing attitudes and behaviours and on implementing and evaluating intervention in the form of awareness campaigns. It consisted of the following:

- Two-stage survey to assess attitudes and behaviour patterns for medicine use and disposal before and after public awareness campaigns.
- Survey to assess attitudes and behaviour patterns (of doctors and pharmacists) for medicine prescription and dispensing.
- Public awareness campaigns over a one-and-half-year time period including actions in schools integrating medical and pharmaceutical professionals and various other stakeholders in the city.
- Information and education campaigns for medical and pharmaceutical professionals.

To capture attitudes and behaviour patterns for medicine use and disposal telephone surveys were conducted in the cities of Dülmen and Soest. The first survey was performed between January and February 2013 with the participation of around 400 households in each of the cities (Dülmen, 47,000 inhabitants and Soest, 48,500 inhabitants). The second survey was conducted in November 2014. In the period between the two surveys, a public awareness campaign was conducted in Dülmen. A similar campaign did not take place in Soest. Thus, the indicative effects of the awareness campaign in Dülmen can be measured through a before-and-after comparison in the two cities.

The two surveys were undertaken by the Rhine Ruhr Institute for Social Research and Political Consultancy, Duisburg, Germany. Inhabitants in the two cities were contacted for a telephone interview. In the first survey some 24% of the estimated 3,300 inhabitants reached by telephone in Dülmen and Soest accepted the request to be interviewed. In the second survey some 31% of 2,572 reached by telephone responded to the questions.

To assess attitudes and behaviour patterns of the medical and pharmaceutical professionals a written survey was conducted in October and November 2013. A total number of 36 (out of 146 approached) medical and pharmaceutical professionals responded to the sent questionnaires, including 5 pharmacists, 24 physicians, 3 clinicians and 4 nurses from care homes.

The awareness-raising campaigns included: discussions with medical and pharmaceutical professionals to share information about the issue of medicines in water; continuing education seminar for medical and pharmaceutical professionals; education projects in schools; a running event and various other events to encourage direct public involvement. Different media were used to communicate the educative information such as newspapers, radio spots, but also flyer, posters and videos on the Internet site of the project and on YouTube.

The findings of this large-scale case study are presented in the following sections, including the effects of the awareness campaigns conducted in Dülmen.

4.5.1 Consumption

With regard to consumption practices it is necessary to distinguish between therapeutic necessity and treatment habits that would also allow non-drug alternatives. In more than half of the households surveyed people with a chronic disease depended on the regular use of medications. Beyond the chronic diseases about 60% of surveyed households had, in the last quarter prior to the survey, health issues that led to the consumption of one or more drugs. 20% of the surveyed households indicated they had not made use of medication in that time period. Medicines used (through prompting) in that time period consisted mainly of analgesic drugs (77.5%)(Fig. 4.6) followed by homeopathic remedies, gastrointestinal agents, antibiotics and cardiovascular agents against beta-blockers, contraceptives, psychotropic drugs, contrast agents and cytotoxic drugs. For more than one-third of respondents (32.1%) the medication was self-prescribed without a prior doctor consultancy (OTC products). In particular, non-prescription drugs with non-opioid analgesics, such as aspirin, ibuprofen, paracetamol and diclofenac were often mentioned. These analgesic drugs are among the most widely sold drugs in Germany.

The households' survey in Dülmen revealed that not all medical / health complaints are treated by pharmaceuticals. In case of conditions such as headache or common colds 29.4% of the respondents were always, or usually, treated with drugs, but more than half of the respondents indicated they rarely cure such conditions with medicines and 14.2% of the respondents indicated that they "never" use medicines to address such issues at all.

Policy pointers:

- OTC medicines make up an important part of pharmaceutical pollution in waters. However, there is apparently good recognition that drug treatment for headaches and colds is not always necessary.

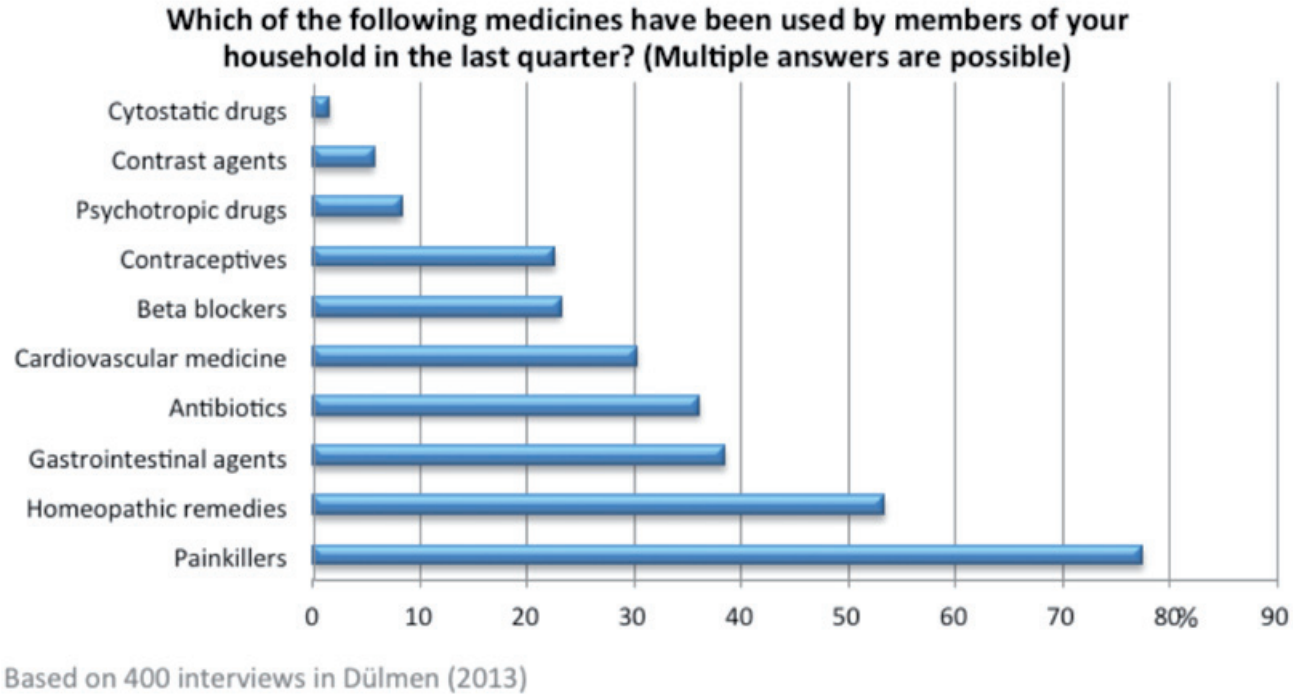


Figure 4.6: The use of medicines by members of the general public

The households' survey in Dülmen revealed that not all medical / health complaints are treated by pharmaceuticals. In case of conditions such as headache or common colds 29.4% of the respondents were always, or usually, treated with drugs, but more than half of the respondents indicated they rarely cure such conditions with medicines and 14.2% of the respondents indicated that they "never" use medicines to address such issues at all.

Policy pointers:

- OTC medicines make up an important part of pharmaceutical pollution in waters. However, there is apparently good recognition that drug treatment for headaches and colds is not always necessary.

4.5.2 Storage and disposal

According to the results of the households' survey about half of the respondents in Dülmen (48.5%) indicated that they stored a maximum of 10 medicines in their medicine cabinet and about 29.1% that the number of medicines they had in the home was between 11 and 20. About 20.8% of the surveyed households had more than 21 medicines in their medicine chest.

The results regarding the frequency of drugs disposal showed a varied picture. About two-third of the surveyed households disposed of drugs from their medicine cabinet after longer intervals, i.e. twice-yearly, annually and even longer intervals. Even though in Germany pharmacies are not obliged to collect unused medicines, approximately 45% of the respondents returned their unused medicines to the pharmacy. About 25% of questioned households disposed of leftover medicines via the residual waste (grey bin), which is incinerated. Almost a quarter of households disposed of leftover medicines via the sink or the toilet into the wastewater at least occasionally (Fig. 4.7). Liquid medication disposal into water was more likely than for tablets, suppositories or ointments. The German-wide percentage of wastewater disposal of unused medicines is even higher than the findings in the Dülmen case study, at around half of (the 2,000 questioned) German households dispose of unused medicines via wastewater (ISOE, 2014).

This group of respondents might be characterized as persons with a lack of awareness about the possible effects of medicine residues in waters. The Dülmen survey also revealed that elderly people appeared to be better informed on the subject than people under 45 years old, and that disposal of leftover medicines via the wastewater originated disproportionately from the latter group, indicating that public awareness campaigns should especially target younger people.

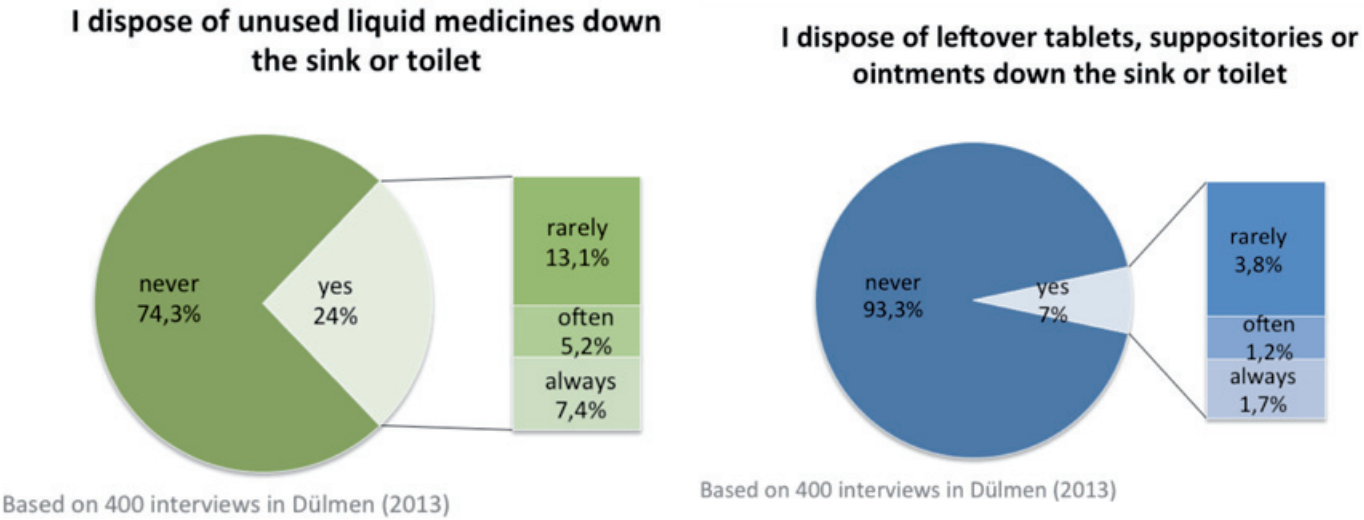


Figure 4.7: Domestic water system disposal of medicines in Dülmen

Policy pointers:

- Leftover medicines are disposed of via wastewater at least occasionally apparently due to the lack of information about the possible impacts on waters. Information about 'good disposal practices' of leftover medicines, might usefully address this.
- Providing information about the possible impacts of drug residues on waters might lead to a proper disposal of leftover medicines. For example newspapers as well as pharmacists and doctors might provide a useful role for this purpose.
- The change of behaviour habits regarding medicine use and disposal might provide an important contribution to the reduction in the emission of pharmaceuticals in the environment.

When asked about possible solutions to reduce the emission of medicine residues in the aquatic environment both, the change of behaviour habits regarding medicine use and disposal and the upgrading of sewage treatment plants by adapted technologies, found high acceptance among the respondents: 86.7% of the respondents deemed advanced sewage treatment as “important” or “very important” to reduce medicines in the receiving waters. Human behavioural change was seen by 98.8% of respondents as “important” or “very important”. A large majority of the surveyed households considered change in behaviour regarding medicine use and the disposal as ‘very important’: 84% in comparison to sewage treatment at 46.5%. This strengthens the assumption that there is an increased willingness of the respondents to be actively involved the reduction of pharmaceutical emissions.

4.5.3 Communication and trust in doctor-patient relationships

Pharmacists and doctors have an important information and advisory task towards patients. The professional expert advice of pharmacists and doctors appears to have been perceived by the patients and medicine consumers in a positive way. The majority of the surveyed households in Dülmen feel they are well informed by their doctor or pharmacist regarding the use of drugs. About 93.5% of the surveyed households rated the professional advice of their pharmacy regarding the use of drugs to be good or very good. Also the professional advice of GPs, as the first medical contact for health problems, was rated by about 97.5% of the respondents to be good or very good.

About 64% of the respondents in Dülmen indicated that in the case of ailments their GPs do not immediately prescribe medicines, with 36% indicating that the doctor did prescribe medication immediately.

A third of the respondents in Dülmen had asked their doctor or pharmacist about non-drug treatment alternatives and, overall, more than half of the respondents were informed by their doctor or pharmacist about non-drug treatment alternatives. So, both patients and doctors seek non-pharmaceutical treatment optionswere.

Policy pointers:

- Advice of pharmacists and doctors is perceived in a positive way by the population and doctors and pharmacists can play a key role for the change of patient behaviour.
- Awareness raising activities might usefully aim at promoting environmentally friendly alternatives recommended by experts such as doctors and pharmacists.
- There is a demand for non-drug treatment alternatives by patients. Such alternatives are proposed in some cases by the medical professionals. Advice on non-drug alternatives should be enhanced in appropriate cases.

4.5.4 Awareness of environmental issues

The appreciation of the ecosystem services provided by rivers in the region and awareness of water contamination by medicines may be important factors influencing attitudes and behaviour patterns regarding medicine disposal into wastewater.

The rivers had high values for the majority of the population. 96% of the interviewed households in Dülmen deemed the rivers as natural goods, which should be preserved in good condition for the following generations. The importance of the rivers as an ecosystem for plants, fish and other species was highly appreciated. The water quality of the river and streams of the region was estimated by 59.6% of the interviewees as good. At the same time almost one-third of the respondents (29%) judged the rivers to be polluted by chemicals.

The pollution of water by medicine residues has received considerable coverage in the press in recent years. The majority of the respondents had heard about water pollution by pharmaceutical residues (64.6% in Dülmen and 72% in Soest, Fig 4.8). But only a minority of the interviewees were aware of the existence of such pollutants in their local rivers.

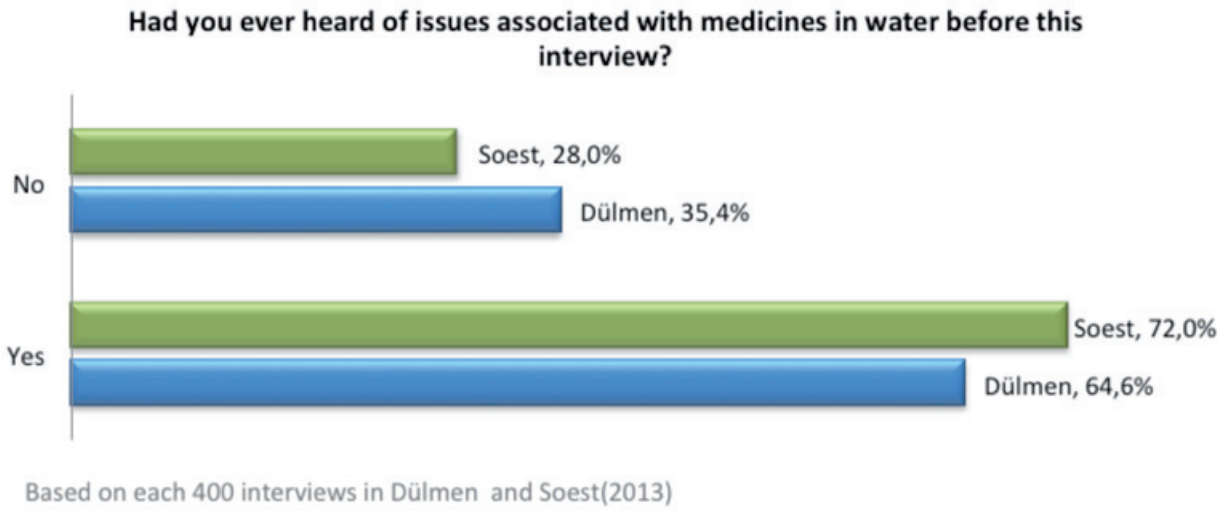


Figure 4.8: Awareness of the issue pharmaceutical residues in water

A clear majority of questioned medical professionals in Dülmen (about 70%) rated the pollution of waters by pharmaceutical residues as a strong ecological hazard. On the other hand, the risk to human health was estimated by about 50% of the respondent medical professionals as relevant. About 30% of the interviewees had been confronted by patients with the issue of pharmaceutical residues, especially in the context of the disposal of leftover medicines.

According to the survey in Dülmen, patients only rarely asked GPs and pharmacists for environmentally friendly medicines. There is a lack of information about such alternatives in Germany. More than half of the questioned GPs and pharmacists stated their willingness to actively support prescription or advice on environmentally friendly medicines in the future if corresponding information is available. The majority of the questioned GPs were also willing to rethink their prescription practice and to support awareness raising actions on this issue.

Policy pointers:

- The protection of waters is of high value for the population.
- Even though the majority of the respondents have heard in general about pharmaceutical residues in waters, there is a lack of awareness about the relevance of the topic in the local situation. Information about pharmaceuticals in the environment should therefore relate to the local water environment to increase its relevance to people.
- There is considerable support for the prescription and promotion of 'environmentally friendly drugs' amongst GPs and pharmacists, but not enough.

4.5.5 Evaluation of awareness campaigns

The effect of the awareness campaigns in the Dülmen case study was evaluated empirically by means of a 'before-and-after' comparison. The situation 'before' represents the households' behavioural patterns in the city of Dülmen without the awareness campaigns. Accordingly, the situation 'after' represents the households' behavioural patterns after the awareness campaigns that were assessed through the use of a second households' survey. Furthermore, the situation 'before-and-after' in Dülmen was also compared to the situation 'before-and-after' in the city of Soest without similar awareness campaigns.

The 'before-and-after' comparison showed that the awareness campaigns reached the target groups in Dülmen. Significant changes 'after' the awareness campaigns were observed in Dülmen as well compared to the situation 'before' in Dülmen itself, as in comparison with Soest. The effectiveness of the awareness campaigns in the case study can be summarized in the following figures:

- 77% of respondents had heard of the individual awareness campaigns.
- 71% of them took notice of at least one of the printed information materials.
- 20% of them actively participated in at least one of the campaigns.
- The fraction of the respondents in Dülmen with knowledge about medicines residues in waters increased by 19%.
- 20% more respondents used the proper disposal way of leftover medicines and 6% less respondents used an improper disposal option in comparison to the situation before awareness campaigns.
- When asked about their own change of behaviour due to the awareness campaigns in the Dülmen, about 34% of the respondents stated they had changed their own habit regarding the disposal of leftover medicines, and 16% of the interviewees claimed to have changed their own behaviour regarding medicines consumption.

Summary:

- Different group-specific activities were carried out to sensitize consumers, pupils and students, GPs and pharmacists on the issue of medicines in waters.
- The awareness campaigns were based on a communication concept that took into account the lack of knowledge about the issue and the perception of the "problem" by the target groups.
- The activities conducted in the case study to raise awareness of the issue were effective.

Policy pointers:

- Pupils and students are good catalysts for awareness raising on the issue inside and outside the school walls.
- Medical and pharmaceutical professionals play a key role for the change of consumers' and patients' behaviour regarding medicines use and disposal.
- A stakeholder analysis prior to the awareness campaigns and the involvement of representatives of the key stakeholder groups in the design of targeted awareness campaign modules is essential for the success.
- Activities for awareness raising should focus on clear messages without using controversy between environment and health.

4.6 Conclusion

Using a range of methodologies the three case studies indicate a clear sense that members of the public, in particular have a considered view on the (over)use of medication. There is a consistent message that they would wish to have more information on appropriate use and disposal, but that this needs to be in an accessible form. This in itself varies for individuals. Equally there is a more general view on the lack of information about appropriate disposal mechanisms, again a common view is held that the existing mechanisms for this are inconsistent and more importantly appear to lack clarity. And yet there is a great desire by members of the public in particular to 'do the right thing'.

5. Reducing emissions of pharmaceutical residues to surface waters by implementing measures of source segregation

5.1 Introduction

An important aim of the noPILLS project was to assess the feasibility and the efficiency of source segregation measures on hospital level. Measures of source segregation can be assigned to the following action listed BIO Intelligence Service (2013):

Action 9: "Assessing the relevance of source separation measures and applying these measures where relevant"

Moreover, a separate collection of pharmaceutical residues can have an impact on the disposal of medicinal products which is an important element of the medicinal product chain (see Chapter 2).

With regard to source separation measures the BIO Intelligence Service (2013) report states that an implementation of measures has to be efficient in view of the elimination of specific molecules and of the local context. That implies a detailed knowledge of the relevant local substance flows and constraints before a source separation measure can be developed and established. In this context the BIO Intelligence Service (2013) focusses on a waste water treatment at source for hospital specific substances like cytostatics or contrast media to reduce emissions to urban waste water systems and subsequent surface waters. Due to the fact that an important amount of substances is administered to ambulant hospital patients or to patients outside of hospitals an import precondition for efficient source segregation is to involve all patient groups.

The results of the previous PILLS project (PILLS, 2012; Kovalova et al., 2012; Helwig et al., 2013; Köhler et al., 2012 etc.) and of earlier studies (e.g. Weissbrodt et al., 2009) indicate the presence of very persistent pharmaceutical substances in hospital waste water and municipal sewage. These substances are not efficiently eliminated by state of the art physical and bio-chemical treatment processes applied in municipal waste water treatment plants. An efficient elimination of these substances by tertiary treatment technologies like advanced oxidation methods is in fact linked to a very high consumption of resources and/or energy. Consequently, Joss et al. (2006) suggest taking into account the degradability of substances to discuss integrated solutions for mitigation like restrictions in use, treatment at source and advanced treatment end of pipe treatment. Segregation and treatment at source should be favoured over end-of-pipe treatment because of several factors reducing the removal efficiency of centralised treatment (e.g. dilution of waste water by extraneous water) (Joss et al., 2006). Furthermore, direct emissions of sewer systems into surface waters by combined sewer overflows can be avoided or significantly reduced by measures at source.

Lienert et al. (2007) showed that a significant amount of numerous administered pharmaceutical substances are excreted via kidneys. Hence, these substances including parent compounds and metabolites are highly concentrated in urine of patients. Consequently, a separate collection and treatment or disposal of urine is expected to be a very effective method to reduce emissions. To achieve this aim a detailed preparation of procedures and a definition of the methodology is required including considerations about relevant substances, social aspects and geographic constraints.

Iodinated X-ray contrast media (ICM) are an example of highly polar and persistent medical substances. A high amount of ICM is administered in hospitals (Weissbrodt et al., 2009). Accordingly, hospitals are one of the major point sources of ICM in urban drainage systems. ICM are of a low toxicological relevance but are found in surface water, ground water and drinking water. (Weissbrodt et al., 2009; IKSR, 2010). Average Concentrations of individual ICM substances vary in the river Rhine for instance from below 0.1mg/l in the source region up to 0.5mg/l at the delta (IKSR, 2010). Maximum Concentrations of up to 30mg/l have been observed in surface waters receiving a high amount of treated municipal waste water like the rivers Ruhr, Lippe and Emscher in Germany (IKSR, 2010).

5.2 Results of source segregation case studies

ICM are predominantly excreted via urine within 24h after administration. Because of their properties and the administered amounts ICM are suitable substances to test segregation measures at source. Accordingly, the separate collection and disposal of urine can be a segregation measure to reduce ICM emissions to urban waste water systems and subsequent surface waters.

A first urine separation campaign to reduce ICM emissions with a focus on stationary patients was implemented in 2005 (Schuster et al., 2006). Two departments of two hospitals in Berlin were involved in the study. The campaign included a procedure of separate urine collection involving the staff of the departments. Monitoring results indicate a reduction of the

total ICM emissions to the urban waste water system during the campaign. Furthermore, the final report of the study includes an evaluation of the acceptance of patients and hospital staff as well as assessments of the mitigation potential and of the costs of a urine separation on hospital level.

In this context the approach of source separation measures is taken up by two national projects in the framework of noPILLS. The project partners Emschergenossenschaft and Luxembourg Institute of Science and Technology implemented urine separation campaigns in collaboration with the radiology departments for their partner hospitals Marienhospital in Gelsenkirchen (Germany) and Centre Hospitalier Emile Mayrisch in Esch-sur-Alzette (Luxembourg). The goal of both case studies was to evaluate the feasibility of a separate urine collection and to quantify the related reduction of ICM mass flows on hospital level focussing on stationary patients (Germany) and on catchment level focussing on ambulant patients (Luxembourg).

In both cases a textile bag was handed out to the target group of patients including an information flyer on the noPILLS project and on the aim of the separation campaign, a set of five urine bags to be used within 24h after getting the ICM injection, a questionnaire to request the gender of the patient, the age class, how many urine bags were used, the patients opinion on the use of the bags, general comments on the campaign and a children oriented book on the topic of pharmaceutical residues in water (see Figure 5.1). The urine bags (KETS GmbH, Germany) include an absorber substance turning the urine into a gel and participating patients were requested to dispose urine bags in the residual waste after use.

Figure 5.1 Female version ladybag® (left image, green bag) and male version of the urine bag roadbag® (left image, silver bag) and set of material handed out to patients participating in the separation campaign

5.2.1. Effectiveness on the level of an integrated waste water system (case study Luxembourg)

The Luxembourgish separation study focused on ambulant patients of the radiology department. Due to that the ICM Iobitridol which is predominantly administered to ambulant patients (ca. 80 % of all patients getting Iobitridol are ambulant patients) was in the centre of interest. Iobitridol which is the active ingredient of Xenetix® is excreted via kidneys and consequently highly concentrated in urine. Following the information provided by the manufacturer of Xenetix (Guerbet, Villepinte, France) about 50 % of the injected load is excreted within 2 hours after injection. The total excretion rate within 24h after injection is about 99 % of the injected dose. During the urine separation campaign multilingual posters presented in the waiting room of the radiology informed patients about the noPILLS project and the urine separation campaign (s. Figure 5.10). Moreover, the staff of the radiology briefly informed patients about the campaign and sent the patients after the scan to collaborators of the Luxembourg Institute of Science and Technology (LIST) located in the waiting room of the radiology. In the waiting room the patients were informed in detail about the campaign and patients willing to participate received the textile bag mentioned above.

Because of a high number of frontier commuters from France, Belgium and Germany and a big Portuguese community living in Luxembourg a quite international patient clientele was expected. Due to this, patients' flyers, manuals for urine bags and questionnaires were available in French, German and Portuguese language. In addition the children's book was also available in Luxembourgish language.

During the 2 week of separation campaign as well as in two reference periods 2 weeks before and 2 weeks after the separation campaign additional data of all patients getting ICM injections were requested in a questionnaire for the staff of the radiology departments. The evaluation of the staff questionnaires provided information on the sex, the age group, the injected ICM dose, if the patient was a stationary or an ambulant patient and the place of residence of ambulant patients. The data allows a calculation of loads expected in the hospital sewer and in the inflow of the downstream municipal waste water treatment plant. In parallel the mass flows of Iobitridol were monitored in the hospital sewage as well as in the inflow and the effluent of the downstream municipal waste water treatment plant of Schifflange. Further details on the monitoring and analytical methods are specified in the appendix. The results of the study are based on a comparison of the expected and observed Iobitridol mass flows on hospital level and on catchment level (inflow of waste water treatment plant).

The partner hospital Centre Hospitalier Emile Mayrisch is the only hospital in the catchment and in the southwest of Luxembourg providing medical scanner services and using the ICM Iobitridol. Therefore, no other sources of Iobitridol are expected.

Results of the survey accompanying the monitoring campaign

During the whole campaign of 6 weeks Iobitridol was administered to 755 patients. In total about 45kg of Iobitridol were administered. Like expected ca. 81 % of the patients were ambulant patients. Figure 5.2 illustrates more detailed information on the patients that received an Iobitridol injecting during the whole campaign of observation. Figure 5.2 shows that the percentage of female patients receiving an injection was slightly above the percentage of male patients. The majority of the patients are older than 60 years and a high percentage is older than 40 years. The number of patients, the percentage of ambulant patients and the administered amount of iobitridol was almost equally distributed among the three periods. In all periods the patients' share of female and male patients and the age distribution of patients was about the same.

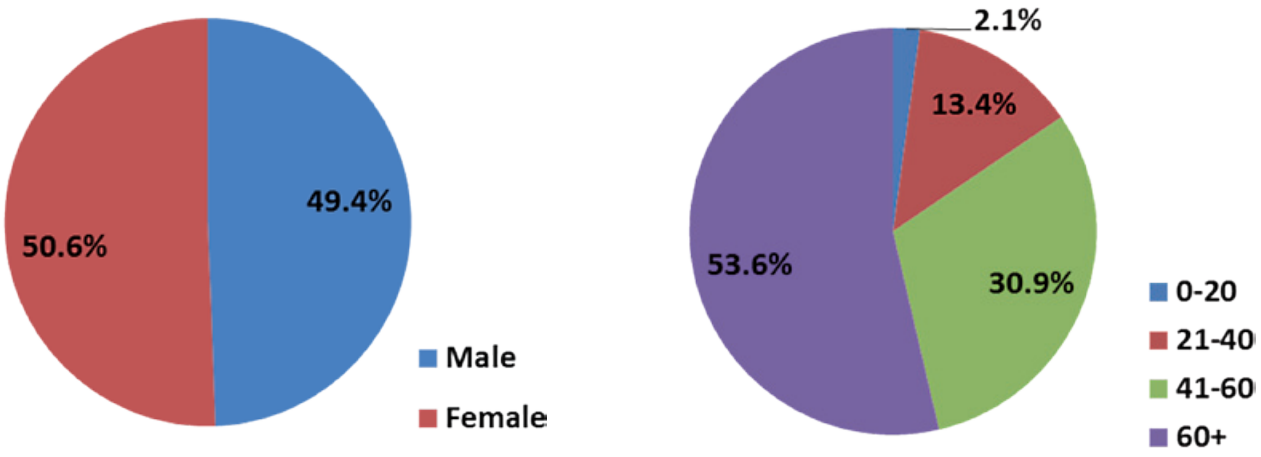


Figure 5.2 Share of female and male patients (on the left) and age classes of patients (on the right) of patients for the whole campaign of 6 weeks

During the two weeks of urine separation campaign 261 patients got administered Iobitridol. A share of 80 % of the patients were ambulant patients (208 patients). About 27 % of the ambulant patients live in the catchment under investigation (70 patients). In total 122 ambulant patients (59 % of all ambulant patients) came to see the collaborators located in the waiting room to ask for detailed information about the separation campaign after the scan. 95 patients (46 % of all ambulant patients) were willing to participate in the separation campaign and received the urine bags. The collaborators of list took notes of the gender of the patients, the language of handed out information (flyers and questionnaires) and of the language of the children oriented book the patients selected.

Results of the patients' survey

A slight majority of ambulant patients that were asked whether they want to participate in the urine separation campaign were female patients (See Figure 5.3). In contrast to this Figure 5.3 also shows that a slight majority of the patients willing to participate in the campaign were male. The individual conversations left the impression that women feel less comfortable to talk about the topic of urinating and using urine bags than men.

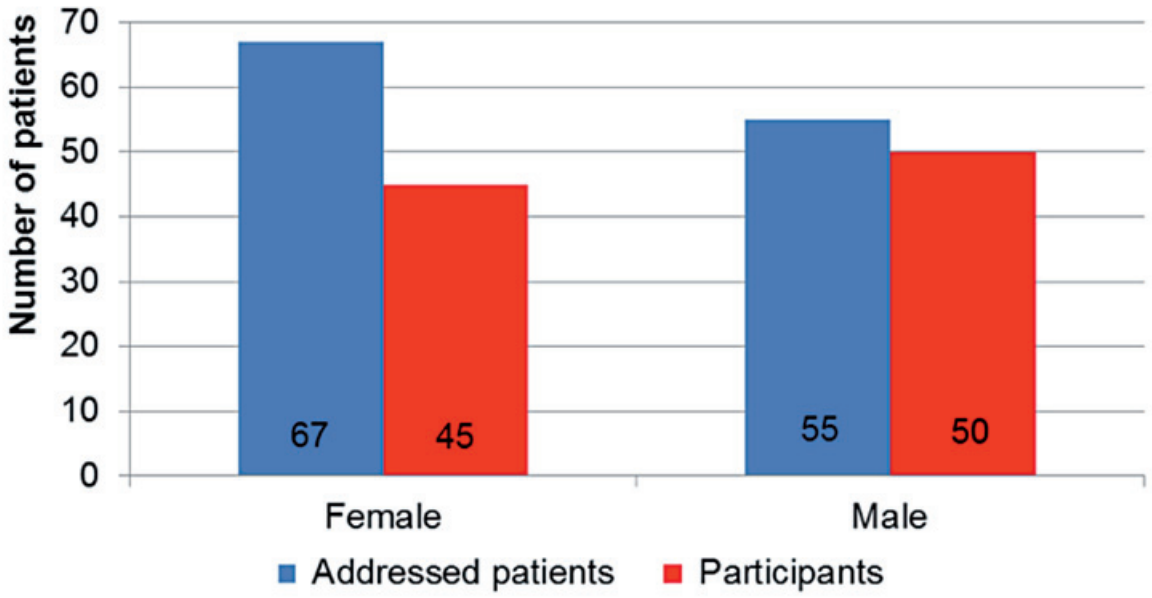


Figure: 5.3 Number and the gender of patients asked whether they want to participate and of patients that agreed to participate in urine separation campaign

Figure 5.4 illustrates the percentages of different languages of the information material and childrens' books handed out to ambulant patients participating in the urine separation campaign, mirroring the different languages and nationalities of the patients of the partner hospital CHEM. About 63 % of the information material handed out to participating patients was in German language (see Figure 5.4). A lower numbers of disseminated information materials were handed out in Portuguese and French language. In contrary to the information material the childrens' book handed out to patients was also available in Luxembourgish language. Expectedly, the language of the handed out book indicates the language spoken in the family circle of the patients. A share of German and Portuguese speaking patients obviously chose the book in Luxembourgish.

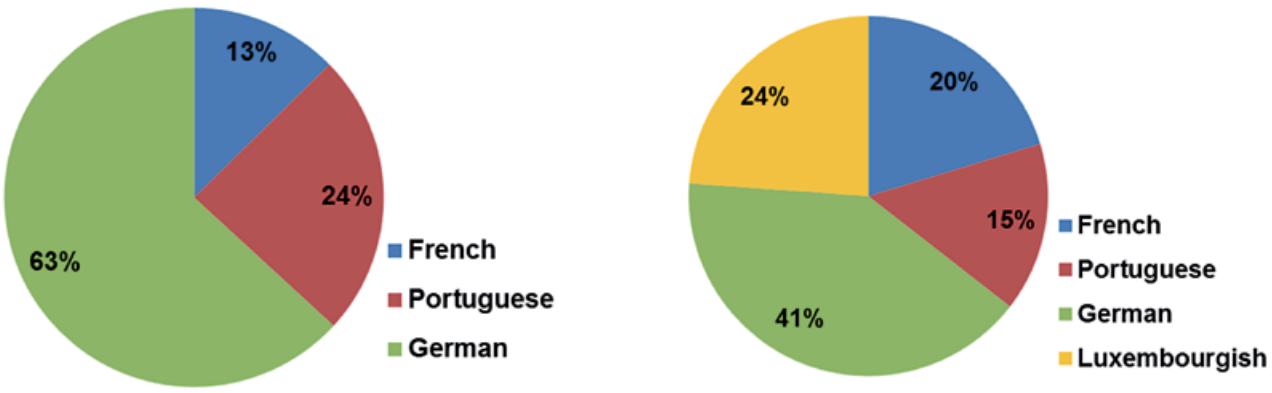


Figure: 5.4 Percentage of different Languages of the information handed out to patients (on the left) and of languages of the handed out childrens' books (on the right).

41 patients participating in the urine separation campaign (43 % of participating patients) returned the patients questionnaire. The percentages of different languages of the returned questionnaires are very similar to the percentages of different languages of the handed out information material (see Figure 5.5). This suggests that the patients returning the questionnaires are a representative group of patients from the native language point of view. A comparison of the age classes distribution of patients returning the questionnaire with the distribution of age classes of all patients getting a ICM injection indicates that especially patients older than 60 years were motivated to participate in the urine separation campaign (compare Figure 5.5 vs. Figure 5.2). This underlines the conclusion drawn in chapter 3 that the target audience of public awareness campaigns should be younger people.

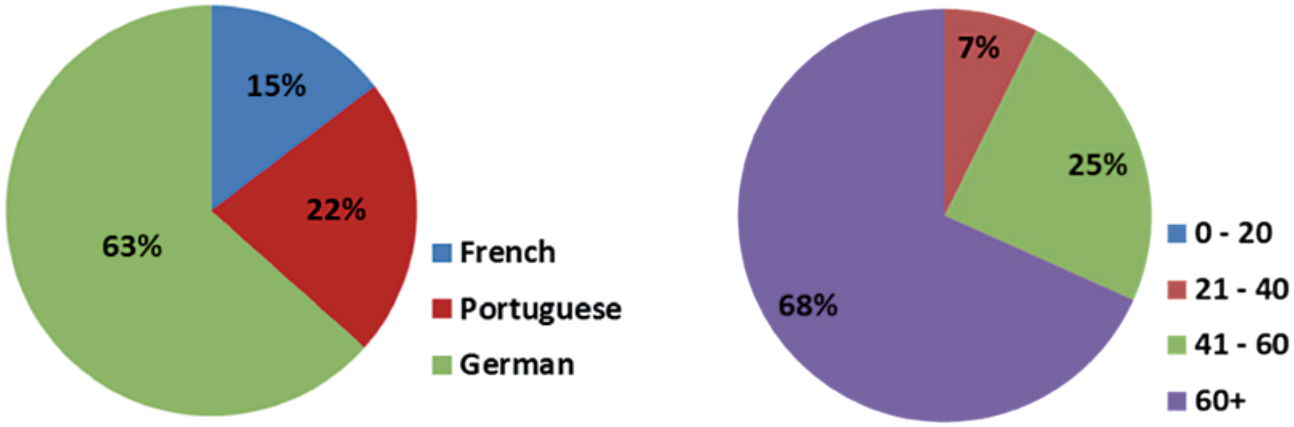


Figure 5.5: Percentage of different Languages of returned patients' questionnaires (on the left) and age classes of patients who answered the questionnaires (on the right)

The number of urine bags used per patients, shown in Figure 5.6, indicates that most of the patients (78 %) used four or all the urine bags included in the urine separation set. However, even the use of 2 urine bags within 2 hours after the injection of ICM would reduce the excreted ICM load by at least 50 %.

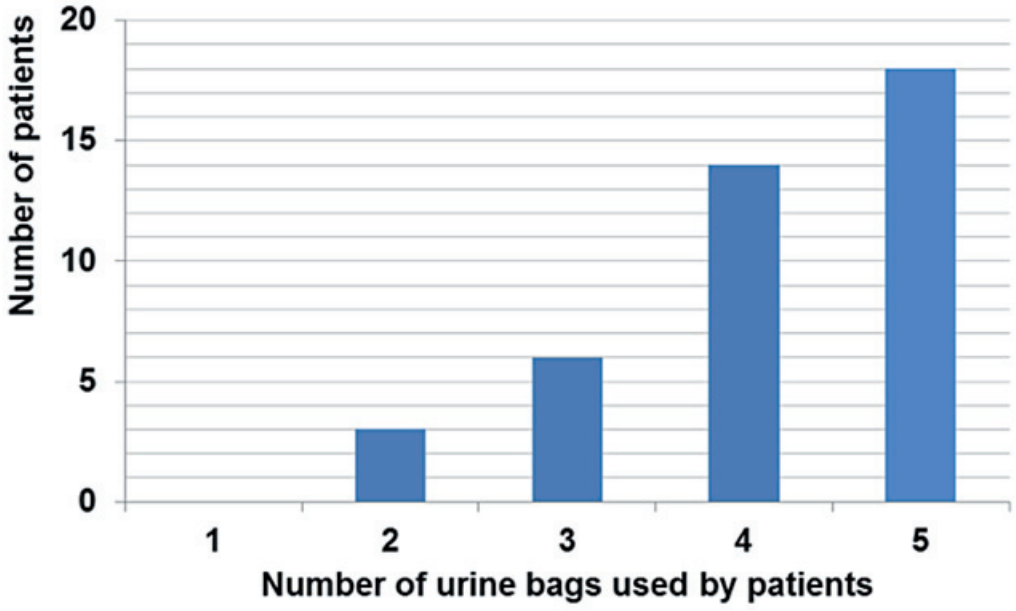


Figure 5.6: Number of urine bags used by individual patients in the urine separation campaign

The final question in the patients' questionnaire focused on the perception of the use of urine bags by the patients (s. Figure 5.7). A large majority of 93 % of the patients shares the opinion that the urine are simple to use. Correlations between the age class of patients and the perception of the use of urine bags or the number of used bags could not be found.

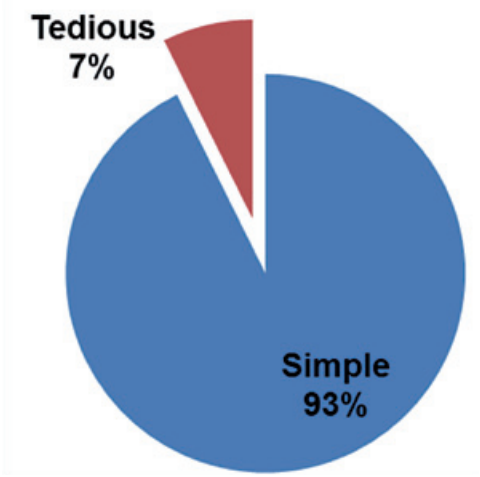


Figure 5.7: Perception of the use of the urine bags

8 of the patients returning the questionnaire added individual comments. Beside comments and recommendations on the use of the urine bags some patients also stated that they strongly support the idea of separate urine collection to prevent pollutions of the environment.

The result of the load balance for the ICM lobitridol in catchment level suggests that not all patients that used the urine bag returned the questionnaire. However, the evaluation of the returned questionnaires provides important and promising information on the opinion of patients about the campaign and on their motivation to participate.

Comparison of expected and observed mass flows

For the calculation of the lobitridol load expected in the hospital sewer it was assumed that the only load contribution is caused by excretions of stationary patients. The comparison of lobitridol load expected to be found in the hospital sewer with the detected load in the three periods of monitoring (reference period 1, separation period, reference period 2) indicate that a significant amount of lobitridol is excreted by ambulant patients in the hospital. This amount is quite constant for all the periods and in average equivalent to 52 % of the lobitridol load excreted by ambulant patients within the first 2h after injection. This leads to the following intermediate conclusions:

1. A lot of ambulant patients urinate in the hospital after lobitridol injection and imaging.
2. Ambulant patients participating in the urine separation campaign did not use the urine bags in the hospital.

Accordingly, although the patients have been told to use the bags also in the hospital if necessary they obviou sly did not feel comfortable to use the bags in an unfamiliar environment for the first time.

A first assumption of the expected lobitridol mass flows from the catchment to the waste water treatment plant included the mass excreted to stationary patients and by ambulant patients on hospital level and the load excreted outside of the hospital by ambulant patients living in the catchment. For the reference campaigns the detected loads on catchment level exceeds the expected load. The additional load corresponds to about 12 % of the load excreted outside of the hospital by ambulant patients not living in the catchment. This implies that a number of persons excreted lobitridol in the catchment that was not administered in the partner hospital or a number of ambulant patients not living in the catchment stayed there for work or for other reasons. For the mass balance on catchment level it was assumed that the additional load during the separation campaign also corresponds to 12 % of the lobitridol load excreted outside of the hospital by ambulant patients not living in the catchment.

Figure 5.8 illustrates the main result of the load balance on catchment level during the separation campaign. It shows the theoretical expected load of lobitridol in the waste water treatment plant inflow that would have occurred without urine separation and the lobitridol load detected. The theoretical expected load was calculated by adding up the lobitridol mass excreted on hospital level by stationary and ambulant patients as well as the load excreted outside of the hospital but in the catchment by ambulant patients living in the catchment and by ambulant patients not living in the catchment. The results show that separate collection of urine caused remarkable reduction of the lobitridol mass flow from the catchment of 17 %. The mass reduction of 1,500g corresponds to 63 % of the mass that was expectedly

excreted in the catchment by participating ambulant patients outside of the hospital. Under the given conditions and taking into account the observed elimination rate of Iobitridol in the waste water treatment plant of 2 %, the implemented separate collection and disposal of urine effects a remarkable reduction of emissions to the urban waste water system and consequently to the subsequent surface water.

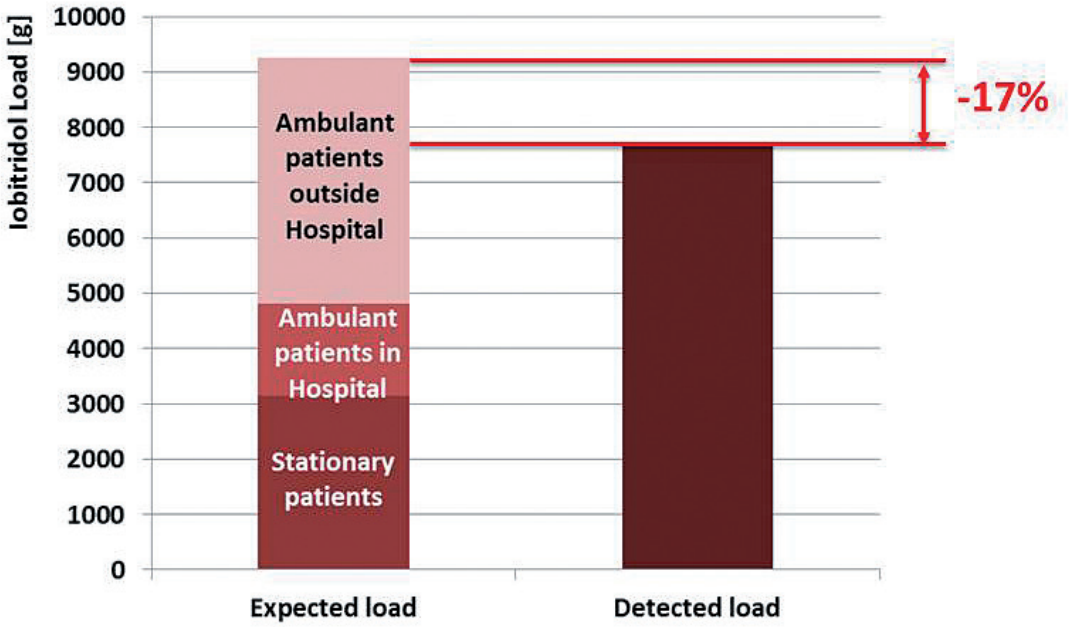


Figure 5.8: Expected and observed mass flow of Iobitridol from the catchment during the urine separation campaign

Figure 5.9 indicates the potential of a comprehensive area wide urine separation at source including a high percentage of ambulant patients. The percentage of Iobitridol mass flow reduction illustrated in Figure 5.9 is related to the total mass of Iobitridol excreted in the catchment. In this context it has to be taken into account that ambulant patients who do not live in the catchment do only partly contribute to the load excreted in the catchment. If all ambulant patients would have participated in the urine separation emissions to the sewer system in the catchment would have been reduced by 66 %. Even if all ambulant patients would only use urine bags outside of the hospital there would still be a reduction of 48 %. Since stationary patients contributed about 33 % to the total mass flow on catchment level during the separation campaign, it is recommended to involve this group of patients into segregation measures at source.

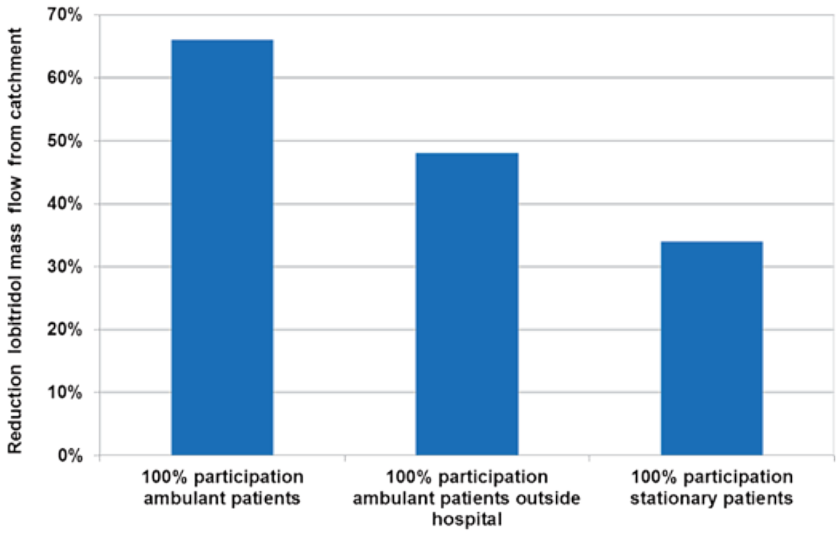


Figure 5.9: Possible reduction of Iobitridol mass flows from the catchment for different scenarios of patient participation

Results of a follow-up workshop with the hospital staff

A final workshop was organised for the staff of the radiology department to present and to discuss the results of the urine separation campaign. 5 Collaborators of the department participated in the workshop (ca. 13 % of the total staff of the radiology). The present collaborators of the radiology were asked to fill in a questionnaire after the presentation of the results of the separation campaign. Among other things they were asked about their knowledge on the effects of pharmaceutical residues in the environment, their perception of the patients' interest in the campaign, their opinion on the campaign. The present staff was also asked if it would be possible to include the procedure of informing patients about urine separation and handing out the urine bags into the routine pre-operative interview with patients before imaging. Further it was requested if they would participate in another separation campaign. The following includes only some results of the evaluation of the survey.

Due to the low rate of participation in the workshop the results presented below do not necessarily provide a representative and complete picture. Presumably, collaborators of the radiology attending the workshop were particularly interested in topics focussing on environment and environmental issues. However, the results give an idea on the perception of the collaborators and on starting points for future communication and implementation activities.

Almost all collaborators of the radiology did now about the fact that pharmaceutical residues are excreted after administration and enter the environment. However, a majority of 60 % did not now about the effects of pharmaceutical residues on the environment before they were involved in the noPILLS project.

In general all collaborators present in the workshop care about environmental issues and are willing to take action to preserve the environment. This is also reflected by the high and very high interest in the noPILLS activities. Asked about their impression of the patients' motivation to use the urine bags, 2 of the collaborators rated the motivation as high and 2 as sufficient. This perception of the staff could be closely connected to the increasable rate of 58 % of ambulant patients that approached the LIST collaborators in the waiting room to get informed about the separation campaign and were asked for their participation.

Other questions of the survey focussed on a possible implementation of urine separation on the level of the radiology department. All of the collaborators involved in the survey would participate in additional urine separation campaigns. However, the majority of the collaborators think that organising urine separation on the level of the radiology would be linked to an additional time effort. 3 collaborators estimate the additional time to be spent on informing patients and handing out the urine separation set at 5 to 10 minutes per patient, but two thought that it does not need additional time.

5.2.2 Effectiveness on the level of a hospital as point source (case study Radiology of Marienhospital Gelsenkirchen, Germany)

The main approach of the German separation case study was similar to the Luxembourgish study: Conducting urine separation using urine bags with CT patients of the radiology department of a hospital for two weeks. The feasibility and the efficiency of the two urine separation weeks were evaluated by a comparison with a reference time of two weeks with normal radiology operation at the hospital. The feasibility was evaluated by a radiology staff survey and a patient survey (questionnaires). The efficiency was additionally evaluated by chemical analysis in the hospital effluent. The following timelines gives an overview on important steps taken by the German case study:

1. 2nd week of September 2014: start of chemical analysis in hospital effluent (reference week)

2. 3rd week of September 2014: start of the separation campaign
   a. Urine bags
   b. Staff survey
   c. Patient survey

3. 4th week of September 2014: separation campaign
   a. Urine bags
   b. Staff survey
   c. Patient survey

4. 1st week of October 2014: chemical analysis in hospital effluent (reference week)

Three samples of the final hospital effluent were analysed for lomeprol in each week resulting in a total amount of 12 samples.

The German separation study focused on patients of the radiology department in the Marienhospital Gelsenkirchen. The ICM Iomeprol (IMERON®) which is predominantly administered was in the centre of interest. Iomeprol is excreted via kidneys and consequently highly concentrated in urine. About 50 % of the injected load is excreted within 2 hours after injection. The total excretion rate after 24h after injection is about 99 % of the injected dose. The German study was mainly adopted from the Luxembourgish project partner. That means not only the urine bags but also the questionnaires were transformed to the German situation. Without this advanced groundwork done by the Luxembourgish project partner the implementation at Marienhospital Gelsenkirchen would not have been possible.

In contrast to the Luxembourgish study, in the German study the radiology department was actively involved and represented the most important partner of the German separation campaign. Prior to the urine separation campaign the radiology staff and related departments of the Marienhospital (healthcare staff at the stations) were briefly informed by the Emschergenossenschaft about the aim, objectives and the proposed

Figure 5.10: Information poster used to inform about the separation campaign at the Marienhospital Gelsenkirchen, Germany

procedure. Additionally, Emschergenossenschaft provided flyers and posters to support the hospital internal information process. Figure 5.10 gives an impression on the way to engage the patients by simple messages.

Furthermore, Emschergenossenschaft provided fully equipped information packages for female and male patients including urine bags, information material, questionnaire for patients to be answered after using the urine bags and mini book. These packages were stored directly in the radiology department.

During the routine pre-operative interview about the ICM treatment at the radiology, the packages were handed out by radiologist to patient if the patient declared the voluntary willingness to participate.

Because of a high number of Turkish speaking people treated at the Marienhospital Gelsenkirchen patients' flyers, manuals for urine bags and questionnaires were produced and provided in German and Turkish language.

During the 2 week of separation campaign data of all patients getting ICM injections were requested in the questionnaire for the staff of the radiology department. The evaluation of the staff questionnaires provided information on the sex, the age group, the injected ICM dose, if the patient was a stationary or an ambulant patient. The data allows a calculation of loads expected in the hospital sewer. In parallel the mass flows of Iomeprol were monitored in the hospital effluent. More information on the monitoring and analytical methods is included in the appendix.

An assessment of the feasibility of a source segregation campaign on hospital level was the focal point of interest of the case study carried out at Marienhospital Gelsenkirchen, Germany. In the case study exclusively patients of the radiology receiving the ICM Iomeprol were involved. Giving the fact that IMERON® (DSS: Imeprol) was also used at other departments at Marienhospital Gelsenkirchen it was assumed that a significant load of Iomeprol remains in the hospital effluent. At the Marienhospital Gelsenkirchen around 50 % of Imeprol is consumed in the Cardiology department (personal information Dr. Keske).

Results of the separation campaign at Marienhospital Gelsenkrichen

During the 2 weeks of urine separation campaign Iomeprol was administered to 156 patients. In total about 11 L of IMERON® (8,67 kg ICM Iomeprol) were administered. Because of their critical physical or mental conditions 94 of these 156 patients could not participate in the separation campaign. The remaining 62 patients (40 %) confirmed their voluntary participation to the radiology staff, which means the participation rate was 100 % (only these 62 patients were asked for participation by the experienced radiology staff). In total 62 information packages were handed over and the radiology staff returned 62 questionnaires to Emschergenossenschaft. Based on the staff questionnaires which include the administered IMERON® dose a total amount of 4.4 L administered IMERON® (3,57 kg ICM Iomeprol) to participating patients could be calculated. This was plausible given the total number of patients and the total amount of administered IMERON® during the separation campaign.

In contrast to the separation campaign implemented in Luxembourg around 80 % of the patients were stationary patients. Slightly different to the Luxembourgish study, almost 75 % of the participating patients were male. Similar to the Luxembourgish results the majority of the patients were older than 60 years.

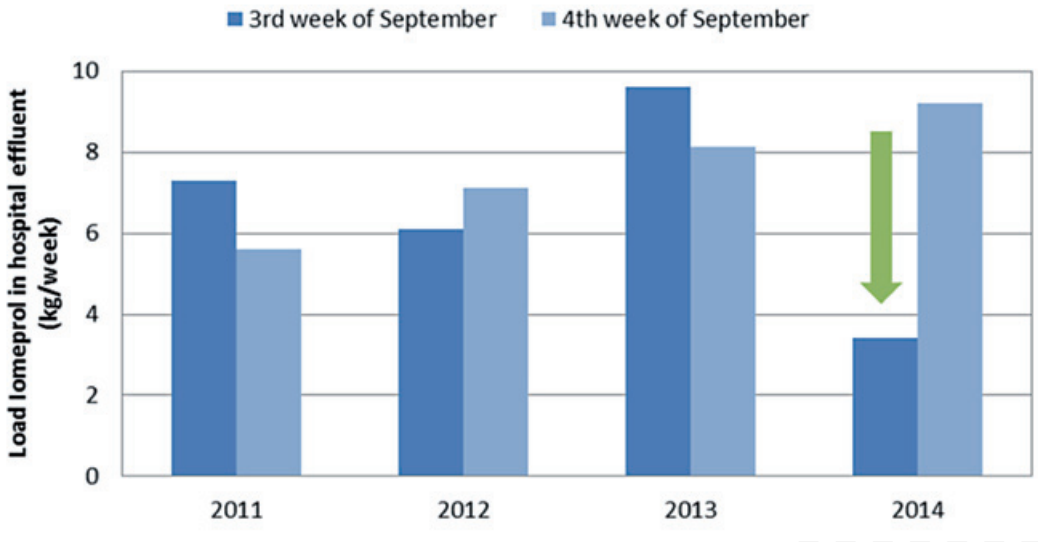


Figure 5.11: Effect of the separation campaign detectable in hospital effluent at the Marienhospital Gelsenkirchen, Germany

From 62 participants in total 20 patients (30 % of all participants) returned the patient questionnaire. It is assumed that at least these 20 patients used the urine bags as the perception with the use of the urine bags was included in the patient questionnaire. All of the returned questionnaires were in German language. 19 of the 20 returned questionnaires arrived in the first of the two separation weeks at Emschergenossenschaft. The post discussions with the radiology staff could not give a reliable reason for the different performance during the two weeks.

Interestingly, the differences could also be detected in the hospital effluents. Almost 50 % reduction of ICM Iomeprol could be detected in the hospital effluent during the first week of the separation campaign in comparison to historical data from corresponding weeks in previous years. In the second week of the urine separation (4th week of September 2014) no significant reduction was observed. The presented data refer to chemical analyses of hospital effluent. The comparison with administered load suffers from the lack of appropriate consumption data. In total 8.67 kg Iomeprol were administered during the two weeks of urine separation. Assuming an equal distribution between the two weeks on weekly consumption of 4.34 kg Iomerol could be calculated. The theoretically administered load of 19 patients returning the patient questionnaire in the 3rd week of September 2014 could be calculated to 1.24 kg Iomeprol.

5.3 Lessons learned

Summary:

- ICM loads administered to stationary and ambulant patients can be significantly different depending on substances used and due to local conditions.
- The separate collection and disposal of urine of ambulant patients (Luxembourg) and of all patients (Germany) resulted in a detectable reduction of ICM emissions on hospital and catchment level.
- Key for the efficiency of the separation campaigns is the active involvement of the medical staff (motivation and engagement of patients).
- It is possible to include procedures needed for separate collection of urine in the routine treatment of patients in radiology departments.
- The estimated additional amount of time to implement separate collection on the level of radiology departments is 5 to 10 minutes per patient.
- There is a clear need to inform the medical staff of hospitals about the environmental effects of pharmaceutical residues in the environment.
- Awareness campaigns should target patients younger than 60 since elderly people seem to be more motivated to participate in separate urine collection campaigns.
- If urine separation gets implemented for all patients (incl. physically or mentally critical stationary patients) a significant reduction of total ICM emissions to surface waters is expected.

Policy pointers:

- Areawide separate collection and disposal of urine of hospital radiology patients can significantly reduce substance flows of Iodinated X-ray contrast media (ICM) to surface waters.
- Separation at source taking the example of urine separation of ICM on hospital level can even work efficiently under difficult boundary conditions (e.g. patients with different native languages and cultural background).
- Results can be transferred to other substances administered in high amounts in hospitals and having similar properties as ICM (excretion path, persistence etc.).
- Measures of segregation like separate collection of urine also offer possibilities to recover specific substances.

6. Occurrence and removal of pharmaceuticals by advanced treatment of hospital wastewater

The applied technologies consisted of full-scale techniques (hospital wastewater treatment plant (HWWTP) Marienhospital Gelsenkirchen consisting of membrane bioreactor (MBR), powdered activated carbon (PAC) and ozonation), pilot-scale techniques (ferrate pilot, MBR pilot, ozonation pilot) and small-scale techniques (biological activated carbon (BAC) columns). These complementary approaches are not only of scientific relevance but also allow the draw of conclusions with practical relevance.

The following technical investigations are collected within this chapter:

1. Long-term monitoring of hospital wastewater
2. Long-term operation of full-scale hospital wastewater treatment plant applying well established wastewater treatment technologies
3. Applying novel technological approaches for the removal of PPCPs from hospital wastewater, using BAC, Ferrate and MBR.

The following questions will be addressed within this chapter:

1. (Temporal) variations of pharmaceuticals in hospital effluents
2. Long-term performance of a full-scale hospital wastewater treatment plant
3. Efficacy of novel advanced wastewater treatment technologies
4. Evaluation of hospital wastewater treatment in comparison to municipal wastewater treatment

6.1 General introduction and objectives

The importance of hospital effluents on a European level is indicated by our previous work (PILLS, 2012) and the BIO Intelligence Service study (2014) on the environmental risks of medicinal products: “For hospital specific substances such as cytostatics, endocrine therapy or contrast media it is shown that hospitals are the overall biggest sources (70-90 %)… [ ] …The implementation of source separation must therefore be efficient for specific molecules and local contexts” (BIO Intelligence Service, 2014; p. 51 ff).

The technological focus of the previous PILLS (2012) project was based on design and construction of waste water treatment plants at hospital locations. Due to time constraints the operation time was limited to the start-up period only. Especially for the biological processes the time frame of the PILLS project prevented the achievement of steady state conditions. The noPILLS project aimed to complement this work with long-term performance studies of the most promising technologies and to address a lack of knowledge on the removal of pharmaceutical micropollutants by MBR or MBR-related processes in different wastewater treatment and reuse schemes (Li, Cabassud, & Guigui, 2014). The noPILLS project allowed extension of continuous operation of the HWWTP Marienhospital Gelsenkirchen to more than four years, and monitoring of hospital effluents before and after treatment provided insight into the performance and efficacy from a practical point of view. This includes the following aspects

- Operational reliability of a decentralized HWWTP
- Emissions (excess sludge, screenings, odor and noise)

Additionally, the continuous monitoring of hospital effluent allows the most profound assessment of hospital wastewater composition and its variation.

These practical aspects are complemented by the investigation of novel treatment approaches for the removal of pharmaceuticals from hospital wastewater. This part is complementary to the previous PILLS project as the applied technologies within PILLS were mainly based on well-established concepts at municipal wastewater treatment plants. To illustrate the connection between PILLS and noPILLS from a technological point of view Table 6.1 – Scheme of the interrelation of technological aspects between PILLS and noPILLS tries to relate open questions of PILLS to the research objectives in noPILLS.

Findings of the PILLS project	Research questions within noPILLS
MBR with excellent removal of pharmaceuticals and metabolites	Long-term stability (HWWTP Marienhospital)
Only partial removal of contrast agents by established advanced treatment techniques	Alternative techniques

Table 6.1: Scheme of the interrelation of technological aspects between PILLS and noPILLS

6.2 Long-term performance of a full-scale hospital wastewater treatment plant: a case of study in Germany

6.2.1 Objectives

The continuous operation of the HWWTP Marienhospital Gelsenkirchen, Germany was accompanied by an extended sampling and measurement campaign. The following issues were addressed:

- Wastewater composition and treatability
- Concentration level of selected (pharmaceutical) compounds
- (Temporal) variations and peak loads
- Achievable effluent quality in long-term
- Assessment of the most persistent compounds in hospital effluents
- Operational reliability of different treatment options

6.2.2 General description of the HWWTP Marienhospital Gelsenkirchen, Germany

A detailed technical description of the HWWTP is given elsewhere (Nafo & Lyko, 2012; Nafo et al., 2012). Developed under the preliminary PILLS project the HWWTP is operated in the designed way. The existing treatment facility is unique for a treatment of hospital waste water with discharge into an open water body.

The HWWTP consists of a combination of a membrane bioreactor (MBR) as a primary treatment step followed by advanced treatment with ozone and powdered activated carbon including a sand filtration step (PAC). Both the ozone and the PAC treatment steps are designed for the total effluent volume of the plant (Figure 6.1).

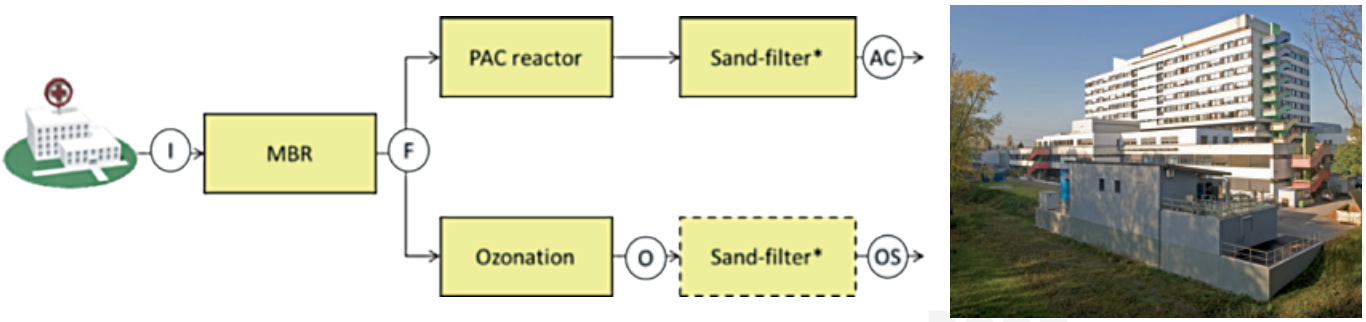


Figure 6.1: Flow scheme and a view of the HWWTP in front of the hospital Gelsenkirchen including the different sampling points I, F, O, OS and AC

6.2.3 Sampling and analytical methods

A continuous sampling and measurement campaign was conducted during the whole period of noPILLS. In total 98 different compounds and parameters were continuously analyzed by the approved joint laboratory of the waterboards Emschergenossenschaft, Lippverband and Ruhrverband. In total, more than 600 time-propotional 24h composite samples were chemically analyzed for micropollutants. The weekly sampling campaigns were organized under consideration of operational issues. As a result samplings were conducted at different week days during the long-term monitoring campaign allowing for an evaluation of weekly variations.

6.2.4 Occurrence of pharmaceuticals in hospital effluents

The hospital effluent composition regarding the analyzed 78 micropollutants can be classified by the frequency of detection:

- Compounds always below LOD
- Compound always above LOD
- Compounds sometimes above and below LOD

Only 20 out of 78 micropollutants could be detected regularly in hospital effluent. The low frequency of detection is explained by the selection of compounds based on the availability of approved analytical methods in the laboratory.

The load of analysed micropollutants in hospital effluents is dominated by contrast agents followed by analgesics and antibiotics. One compound – the ICM Iomeprol – represents more than 92 % of the total load of micropollutants in the hospital effluent of Marienhospital Gelsenkirchen, Germany. Together analgesics and antibiotics represent only 2 % of the total load of micropollutants in hospital effluents. This is in good agreement with the general composition of European hospital effluents (Verlicchi, Al Aukidy, Galletti, Petrovic, & Barcelo, 2012; Verlicchi, Al Aukidy, & Zambello, 2015primary, secondary and polishing; Kovalova, Siegrist, Singer, Wittmer, & McArdell, 2012). With the macrolide antiobiotics hospital wastewater contains significant concentrations of compounds which are included in the watch list of the EU Priority Substances Directive (Carvalho, Ceriani, Ippolito, & Lettieri, 2014). Whereas the macrolide antibiotic erythromycin was detected in lower concentration range the human metabolite dh-erythromycin exceeds the concentration of the parent compound by a factor of two.

A more or less stable composition of hospital effluents was observed during the long-term monitoring at Marienhospital Gelsenkirchen, Germany. Weekly variations can be neglected. This is a strong indicator for a more or less stable hospital operation. Only for the contrast agent iomeprol a trend to lower consumption on Friday seemed to occur. This is in good agreement with the operation at the Radiology department of the Marienhospital Gelsenkirchen. At weekend only cases of emergency are treated (Keske, 2015). In general the results of the intensive monitoring within the previous PILLS project could be confirmed (Nafo et al., 2012).

There was no seasonal variation for antibiotics in hospital effluents. The tendency to higher concentrations in winter (Verlicchi, Al Aukidy, Galletti, et al., 2012) could not be confirmed. This is also different to recent findings for raw municipal wastewater (Petrie et al., 2014; Kaeseberg e al. (2015). A pronounced seasonal variation of selected antibiotic compounds and a strong correlation with the frequency of respiratory diseases was found by the R&D project Anti-Resist (Mühlbauer, 2014; Marx and Kühn, 2014; Hutka et al., 2014). Using GoogleFlu® data a strong correlation between frequency respiratory diseases and antibiotic consumption was found for municipal wastewater of the city of Dresden (Hutka et al., 2014). Such a strong correlation could not be confirmed for the effluent of Marienhospital Gelsenkirchen. Only a few antibiotic compounds (clarithromycin, ciprofloxacin, azithromycin, trimethoprim) showed a slight tendency to higher concentrations in winter time (r^2<0,12). If this indicates an specific difference between domestic and hospital effluents was to be confirmed by additional monitoring campaigns.

Additional research is needed to verify the effect of short distances between hospital effluent production and HWWTP influent. From urban wastewater system it is known that remarkable degradation and transformation processes occur in the sewer system. In that respect it is likely to expect differences between the influent of urban WWTPs and hospital WWTPs. This specific issue was beyond the scope of the PILLS and noPILLS project

6.2.5 Long-term process performance of the full-scale HWWTP Marienhospital Gelsenkirchen

Background information on the design values and some key process parameters are given elsewhere (Nafo & Lyko, 2012; Nafo et al., 2012). Since the start-up in April 2011 the HWWTP was continuously operated for more than four years. The MBR treatment step was necessary to ensure the required effluent quality for direct discharge into the nearby river Schwarzbach. Therefore, the MBR treatment was - and still is - continuously operated for the whole time. The advanced treatment steps were periodically operated according to specific research questions. During that time a total amount of more than 109,000 m^3 hospital effluent were treated in the HWWTP. The resulting average flow rate of 76 m^3/d was lower than the maximum design value of 200 m^3/d. The operation of the MBR was quite stable. The biological design values for organic and nutrient removal were always overachieved. The mixed liquor suspended solids concentration (MLSS) in the bioreactor was kept constant within the designed range

between 8 and 12 g/L. Due to the lower average flow and due to the designed buffer volume in the bioreactor a significant lower biomass growth and subsequent a very low sludge production occurred. This was in favour of the residual management as less excess sludge has to be removed from the HWWTP. The excess sludge was transported by trucks on the road to a nearby urban WWTP. There it was mixed with the thickened digested sludge. Passing the existing sludge treatment the mixture of hospital and municipal sludge was finally incinerated.

During the four years of continuous operation the average temperature within the biological reactor was 26°C. The stable and relatively high hospital effluent temperature supported the biological process performance. Due to the boundary conditions at the Marienhospital Gelsenkirchen the MBR treating hospital effluent was overachieving in comparison to MBRs treating municipal wastewater.

The biological treatment process was mainly controlled by the oxygen concentration in the bioreactor. In general, the transferred oxygen by the crossflow aeration of the flat-sheet membranes was sufficient to ensure a complete nitrification and organics removal. In order to prevent clogging and to control fouling of the submerged membranes a certain aeration rate is required. By an adapted operation regime consisting of recirculation loops the biological reactor can be effectively operated as a denitrification zone. The efficiency of this operation strategy can be seen by a stable pH in the bioreactor and by the good effluent quality regarding classical wastewater sum parameters like COD, N and P. Furthermore, disinfection by membrane filtration ensured bathing water quality in terms of microbiological parameters. These sum parameters are unaffected by additional treatment technologies. Thus, biological transformation represents the major treatment process to achieve the required effluent quality for direct discharge into the nearby surface water body. A scientific discussion of the long-term process performance is in preparation.

6.2.6 Elimination of micropollutants by the HWWTP during long-term operation

The total load of analysed micropollutants can be significantly reduced by the HWWTP. The main load of micropollutants was removed in the MBR step. Almost 95 % of the total load of micropollutants can be removed by the MBR treating hospital effluent.

It is known that higher removal efficiencies were achieved by MBRs (Verlicchi, Al Aukidy, & Zambello, 2012). Nevertheless, the results of the HWWTP Marienhospital Gelsenkirchen were significantly overachieving in comparison to MBRs treating municipal wastewater (Verlicchi, Al Aukidy, & Zambello, 2012). In fact, this could be considered as long-term proof of

Substance class	Hospital effluent (g/d)	MBR effluent (g/d)	Ozonation effluent (g/d)	Final effluent (g/d)
X-ray Contrast Media	1266.9	32.4	28.6	26.0
Analgesic	10.7	0.2	0.1	0.1
Antibiotic	5.2	0.7	0.3	0.3
Betablocker	1.1	0.1	0.1	0.1
Musk Compound	0.5	0.1	0.0	0.0
Disinfectant	0.2	0.1	0.0	0.0
Lipid Regulator	0.2	0.0	0.0	0.0
Antiepileptic	0.1	0.1	0.0	0.0
Beta 2- Adrenergic Receptor Agonist	0.0	0.0	0.0	0.0
Drugs for acid related disorders	0.0	0.0	0.0	0.0
Psycho-active Drug	0.0	0.0	0.0	0.0
Total	**1284.9**	**33.7**	**29.1**	**26.5**

Table 6.1: Average load of analysed micropollutants substance classes in the HWWTP Marienhospital Gelsenkirchen, Germany

similar results in the previous PILLS project. Even with some differences in the removal for different substance classes the general removal behaviour stayed the same: the main removal occurred in the MBR and the remaining compounds in MBR effluent can be further reduced by the advanced treatment steps ozonation and PAC. There were no significant differences in the treatment efficiency of advanced treatment by ozone or activated carbon.

From the analysed micropollutants the most persistent compounds, being detectable above 0.5 µg/L in the final effluent, are only 6 iodinated contrast agents (ICM). Even with high elimination rates above 90 % in MBR some compounds are still detectable because of very high concentrations in the hospital effluents (e.g. galaxolide, .tonalide, metoprolol, iomeprol, clindamycin, vancomycin, ciprofloxacin).

Compounds included in the watch list are removed by the MBR step. Especially the macrolide antibiotitics showed remocal rates above 80 %. For the persistent analgesic Diclofenac the MBR removal was 60 %. It should be considered that Diclofenac was of minor relevance in the hospital effluents of Marienhospital Gelsenkirchen (only 0.7 % of the total load of anaylsed micropollutants without contrast agents). A scientific discussion of micropollutant removal in the HWWTP is in preparation.

6.2.7 Energy consumption and emissions of a full-scale HWWTP

The energy consumption of the HWWTP is dominated by the MBR step (2.51 kWh/m³) and the exhaust air treatment (2.90 kWh/m³). For the MBR step the value is doubled in comparison to municipal MBRs. This can be explained by the enormous energy demand for the crossflow aeration of the membrane modules. Due to severe clogging and subsequent damage of the modules optimization of the crossflow aeration could not be achieved during the long-term operation. In contrast the damage of the modules required the exchange of membranes and the re-installation of new membrane modules. As the characteristics of the MBR sludge of the HWWTP are similar to municipal MBR sludge an explanation of the severe clogging is still to be found. The supplier of the membranes supports the investigations on that issue.

The air treatment was a requirement by the authorities because of the HWWTP site directly opposite the hospital. It consists of a combined advanced oxidation process (AOP) and activated carbon adsorption process able to disinfect the exhausted air before discharging into the atmosphere. An extensive sampling and measurement campaign was conducted to monitor the effect of the air treatment in terms of organics, odour and corrosion agents. Therewith it could be proved that the exhaust air of the HWWTP is comparable to exhaust air of municipal WWTPs. These results provide the base for future discussions with the responsible authorities about an optimized operation of the air treatment at the HWWTP.

The energy consumption of the advanced treatment step PAC-SF (0.49 kWh/m³) is comparable to the application of that technique at municipal WWTPs. It is dominated by the energy demand of the sand filtration which is required to separate the loaded PAC from the treated wastewater. The energy consumption of the advanced treatment by ozone (2.63 kWh/m³) is significantly higher than at municipal WWTPs. This is explained by the different mode of ozone production. Due to the smaller size of the HWWTPs it was not economically feasible to provide a liquid oxygen periphery. Especially the usage of large oxygen storage tanks is limited due to space restrictions at hospitals. Therefore, the pure oxygen had to be produced onsite. This process consisted of air compression followed by pressure swing absorption and subsequently increased the energy demand of the total process of ozonation at the HWWTP.

The emissions of odour and noise could be easily managed at the HWWTP. Even though the HWWTP was operated in a distance of only 10 m to the medical intensive treatment of the hospital there was not any related issue documented during the total operation period of more than four years neither from the hospital management nor from the patients. In contrast very positive feedback was achieved.

6.2.8 Summary and policy pointer

The continuous operation of the full-scale HWWTP was supported by a comprehensive monitoring of standard wastewater parameters and micropollutants like pharmaceuticals, personal care products and contrast agents. This represents the realistic and well-founded assessment of the source hospital effluent and its decentralized treatment option:

Summary:

- Except for the solids and particles load hospital wastewater is comparable to domestic wastewater in terms of standard wastewater parameters.
- Source separation of rain water is very efficient at hospitals.
- The substance class of contrast agents dominate the load of micropollutants in hospital effluent.
- Beside contrast agents analgesics, and antibiotics are the two substances classes with the highest load in hospital effluents.
- Seasonal variations are less pronounced in the hospital effluent of Marienhospital Gelsenkirchen compared to domestic wastewater.
- Successful, continuous operation of a sophisticated wastewater treatment plant at a hospital was achieved.
- The comparison between the HWWTP Gelsenkirchen and several full-scale municipal WWTPs of the waterboards Emschergenossenschaft and Lippeverband shows better treatment efficiency but higher energy consumption.
- The following challenges for the decentralized hospital wastewater treatment remain:
  - Hospital waste disposal in the sewer system (causing damages)
  - Organisation of the operation
  - Co-financing of the treatment under current legislative boundaries

Policy pointers:

- Hospitals are a remarkably large source of contrast agents.
- The separate collection of different wastewater streams at hospitals is possible and economically feasible.
- Hospital wastewater can be collected prior to dilution in the sewer system.
- Experiences from municipal wastewater treatment can be transferred to hospitals.
- Decentralized treatment of hospital effluents on-site is operationally reliable.
- Disinfection by the ultrafiltration step of the MBR is possible.

6.3 Removal of pharmaceutical residues in a biologically pre-treated wastewater using Biological Activated Carbon (BAC): a case of study in Luxembourg

6.3.1 Introduction

During the previous PILLS project, the Luxembourgish Institute of Science and Technology (LIST) PP3 was in charge of assessing the performance of well-known advanced treatments such as Ozonation, Reverse Osmosis, UV and advanced oxidation processes (AOP) at decentralized level. More details on the Luxembourgish pilot set up are given in Köhler et al. (2012) and Venditti et al. (2012).

All these treatments were installed to further treat a hospital effluent after an initial biological degradation in a Membrane Bio-Reactor (MBR). The pharmaceutical residues remaining after the MBR were eliminated to a high degree by all the technologies listed above. However, the high energy consumed and operational costs together with the potential to produce additional toxic products (i.e. bromate in the case of Ozone) have to be taken into account (Magdeburg et al., 2013; Margot et al. 2013). The need to propose technical solutions more sustainable was thus driving LIST to the idea of testing a more 'passive' and somehow ambitious technology, as Biological Activated Carbon (BAC). Pharmaceutical residues, as well as microorganisms, are eliminated, first of all, by sorption to activated carbon. An active-biofilm formation then allows residues to be further reduced through biodegradation (Reugoat et al., 2011; Rattier et al., 2012). This technology constitutes a very interesting solution, both in terms of its efficiency and its lifetime as the GAC column run further after it is exhaused for sorption capacity.

6.3.2 Methodology

The pilot-scale Membrane BioReactor (MBR) plant in Esch-sur-Alzette (Luxembourg) runs continuously to treat hospital wastewater on-site from the Centre Hospitalier Emile Mayrisch (CHEM). The pilot plant consists of a mechanical step (fine sieve), two biological steps (anoxic and aerobic zone) with submerged flat sheet membranes , and a post-treatment with Granular Activated Carbon (GAC). Five pilot-scale GAC columns were set up in order to investigate the removal of target pharmaceuticals present in the hospital sewage. The five columns were operated in up flow mode and fed in parallel with MBR effluent at different Hydraulic Loading Rates (HLR) ranging from 8 m/h (column 1) to 1 m/h (column 5) and linked Empty Bed Contact Times (EBCT) ranging from 4 min (column 1) to 33 min (column 5). Details on operational conditions of the pilot scale study and on excretion pathways of the selected pharmaceuticals are given in the annex.

6.3.3 Sampling and protocol analyses

Pharmaceuticals were chosen considering those known to be excreted in the highest amount (calculated considering the consumption of active ingredient) in the CHEM hospital and with the highest eco-toxicity, expressed as Predicted No Effect Concentration, PNEC.Compounds are listed in Table 6.2. The assessment of the BAC as tertiary treatment was carried out following three main sampling campaigns focusing on the MBR performance, evaluating the elimination rates in GAC / BAC and the characterisation of the biofilm.

6.3.4 Assessment of the BAC: results

During the operation time, the MBR was generally ensuring a stable quality influent to the BAC columns with a consistently high COD and TN removal efficiency of 94 % and 62 %, respectively, and absence of suspended solids. The MBR elimination efficiency of pharmaceuticals ranges widely depending to compound specific characteristics such as biodegradability, absorbability and their formation potential from metabolites. In comparison to the treatment efficiency of the MBR Marienhospital Gelsenkirchen (German cas study of PP1) lower elimination rates were observed. Only the analgesic Naproxen was removed up to 80 %. Most of the compounds were removed between 50-80 %.

Several compounds, including the X-ray media Iobitridol, showed low elimination efficiencies. The enrichment of the antibiotic Sulfamethoxazole in the effluent which results in a negative elimination rate, can be explained considering that Sulfamethoxazole is excreted in an acetylated form which reverts to its parent compound during the biological treatment as observed by Göbel et al. (2005). Erythromycin and Fluorouracil were below the limit of quantification (LOQ) in the hospital wastewater. Treating pharmaceuticals at their point source clearly improves antibiotic removal, but the concentrations are still significant and advanced treatments are considered necessary.

The performances of BAC are thus evaluated in terms of organic matter and micropollutants removal. The DOC content in the BAC effluents was always lower than in the influent. A general common trend independent from operating conditions can be observed. The DOC removal was asymptotically diminishing with time. Initially, most of the DOC removal (i.e. around 40 % during the first 100 days) occurs through physical adsorption of the DOC to the GAC media when the bacteria in the associated biofilm are still adapting.

Once the bacteria are acclimated, DOC removal by adsorption gradually decreases (i.e. around 20 % for the next 100 days) as the GAC sites become saturated with DOC. During this period, the two processes of adsorption and biodegradation are coexisting and it is difficult to quantify one or the other. Of the total DOC removed, 10-20 percent of the DOC is believed to be non-adsorbable on the GAC according with Dussert and Van Stone (1994). In a last period, when the GAC is saturated and breakthrough of DOC has been reached, the rate of the DOC removal reaches relatively steady state with a low removal (i.e. less than 20 %). In this phase the biological degradation is the predominant process.

Regarding micropollutants different behaviors can also be observed but expected to show a similar trend of the DOC depending to factors such as matrix, competitiveness and individual adsorption properties of each compound.

Information about final breakthrough of each compound is summarized in 6.2. Generally breakthrough of every compound seems to occur between 4 and 5 months of operation. For Clarithromycin the behavior is independent from operation conditions of the columns (i.e. flow rate and thus contact time EBCT) but for most of the others a longer EBCT ensure a better

performance of the column with higher elimination rate, less fluctuation and more stability. X-ray contrast media showed individual behavior depending on their sorption affinity. Iobitridol (MW=835) did not show any breakthrough but a continuous and stable elimination during all operation time, whereas Iodixanol (MW=1550) depicted an early breakthrough and high fluctuation as other X-ray in literature (i.e. Iopromide).

During the operation of the columns, two events related to the malfunctioning of the MBR were observed. A cleaning of the Kubota membranes resulted necessary twice, after 77 and 183 days of operation. A failure on the MBR was affecting the quality of the BAC influent with presence of total suspended solids and high nutrients able to develop a biofilm clocking the columns.

For this reason, few peaks in concentrations were observed right before the cleaning of the membranes and a more frequent backwash of the columns was required.

This problem was known already during PILLS when the relatively bad quality of the MBR permeate for Ozonation and UV influent water was somehow compromising the efficiency of these two technologies. BAC required much less energy for its own functioning. A scientific discussion of BAC results is in preparation.

Group	Compound	Breakthrough		Degradation due to biofilm [%]
		Cfin / Ci [%]	(days of operation)	
Antibiotics	Amoxicillin	25 (C1) -15 (C5)	154	20
	Ciprofloxacin	76 (C1) – 9 (C5)	107 (C1-C3) – 121 (C4,C5)	10-20
	Clarithromycin	58 (C1) – 94 (C5)	121	30
	Erythromycin	n.d.	n.d.	n.d.
	Sulfamethoxazole	n.d.	n.d.	n.d.
Anesthetics	Lidocaine	30 – 1 (C5)	121*	n.d.
Analgesics	Diclofenac	60 (C1) – 7 (C5)	121	20
	Naproxen	70 (C1) - 11 (C5)	121, 167 (C5)	20
Anticonvulsant	Carbamazepine	70 (C1) – 10 (C5)	121, 167 (C5)	n.d.
Cytostatics	Cyclophosphamide	20 (all columns)	121*	n.d.
	Fluorouracil	n.d.	n.d.	n.d.
X-ray media	Iobitridol	< 20	n.d.	n.d.
	Iodixanol	80 (C1) – 1 (C5)	35	n.d.

Table 6.2: Elimination of pharmaceuticals in the BAC configuration
Cfin: Final concentration of column effluent (after saturation)
Ci: Concentration of inflow to columns
C1: Column 1; C2: Column 2; C3: Column 3, C4: Column 4; C5: Column 5 n.d.: not detected

6.3.5 Summary and policy pointer

Summary:

- Granular Activated Carbon applied to hospital wastewater constitutes an efficient measure to treat pharmaceutical residues at relatively low effort in terms of energy consumed.
- The use of active biofilm to further degrade micropollutants after an initial sorption phase does prolong the life time of conventional GAC versus more innovative Biological Activated Carbon (BAC).
- Results of biofilm characterization have to be analyzed and a better conclusion addressed on the thematic.
- Further aspects of BAC operation and the microbiological degradation in the biofilm need to be investigated like the potential of biological regeneration of GAC.

Policy pointers:

- Optimised and innovative treatment approaches can reduce resource and energy consumption of advanced treatment systems.

6.4 Decentralised and centralized treatment options of hospital effluents: a case study in France

6.4.1 Objectives

Two partner hospitals supported the French case study within noPILLS: Limoges hospital and Bellecombe Hospital (Hospital Center Alpes Leman – CHAL).

The Limoges hospital part, built on a well-established cooperation between the Hospital (CHRU – Regional University Hospital) and the University of Limoges (France), was to investigate the assessment of health and environmental risks associated with micropollutants in water, particulary antibiotics and antibiotic resistance. This included an investigation on the receiving Limoges WWTP and a study of improving the performance of existing stations by different treatment methods (activated sludge processes CAS and MBR, addition of carriers for biofilm development (MBBR) and ozonation) at pilot scale with a particular research on microbiology of the activated sludge and the overall efficiency of the WWTP.

The CHAL part evaluated, on the watershed of the Arve (a tributary of the Rhone that comes from the Western Alps in France and discharges in Switzerland close to Geneve into the Rhône), the impact on water resources, discharges of micropollutants from wastewater treatment plants. PP6 cooperated with the management of the waste water treatment plant. This work, in collaboration with the Observatory of the SIPIBEL project, focused on the qualitative and quantitative characterization of micropollutants in biological sludges and in antibiotic resistant bacteria.

6.4.2 Upgrading an activated sludge system for the treatment of hospital effluent

The objective of the study was to improve the performances of activated sludge treatment plants and to apply them to the treatment of hospital wastewater. Different types of biological reactors were investigated:

- Conventional Activated Sludge (CAS)
- Membrane Bioreactor (MBR)

- Moving Bed Biofilm Reactor (MBBR)
- Ultrafiltration system (AS-UF)
- Moving Bed Biofilm Reactor coupled ultrafiltration (MBBR-UF)
- Moving Bed Biofilm Reactor coupled ultrafiltration and granular activated carbon (BBR-UF-GAC)
- Classical Activated Sludge coupled with ozonation (CAS-O_3)
- Returned activated sludge ozonation (RAS-O_3)

6.4.3 Results and discussion

The following table reports the removal for selected compounds at the different pilot designs:

Compounds	CAS	MBR	MBBR	AS-UF	BBR-UF	BBR-UF-GAC	CAS-O_3	RAS-O_3
Bezafibrate	5.6	100						
Paracetamol	99.4	99.6	98	100	100	100	100	100
Atenolol	95.4	93.9	97	100	75	100	98	
Cyclophosphamide	0	88						
Sulfamethoxazole	0	87.4	91	95	100	100	98	100
Ifosfamide	99.4	80.5						
Naproxen	0	48.3	95	85	95	100		
Iopromide	0	46.4		100	75	100		
Carbamazepine	46.9	-	83				80	100
Diclofenac	20.9	0	68	++	30	100	100	100
Iomeprol	0	0	96					

Table 6.3: Removal for the different designs of reactor (%)

For CAS the highest removal efficiency (95± 5%) or a complete removal could be observed for paracetamol, atenolol, ifosfamide and a partial removal for carbamazepine and diclofenac, bezafibrate, cyclophosphamide, sulphametoxazole, naproxen and iopromide were not eliminated. The addition of a membrane, whether internal or external, allowed the removal of bezafibrate, cyclophosphamide, sulfamethoxazole and, but only partially, naproxen, iopromide, carbamazepine and diclofenac. The addition of carriers in the reactors has improved the yields certainly favouring firstly the sorption, and secondly, by increasing the biofilm and thus improving biodegradation. It was the case for sulfamethoxazole and naproxen, but not for diclofenac. The total removal of all the tested substances has been reached when the column filled with GAC has been added.

In terms of processes, carriers added to the activated sludge basin (MBBR) stabilized the activated sludge treatment process and reduced membrane fouling.

The removal obtained for the biological system coupled with tertiary ozonation (CAS-O_3) was excellent even with low doses of transferred ozone (4 - 5 mgO_3/L). Average removal rate of 92% was obtained for

10 pharmaceutical compounds with only a efficiency of 70 % for econazole (data not shown).

Sludge ozonation was effective for the oxidation of adsorbed compounds on sludge flocs. It was also noted that sludge ozonation resulted in both a reduction of suspended solids (SS) content due to solubilization the particulate organic matter and the removal of parent compounds (no investigation on the formation of transformation products). A cross-analysis of the results was conducted and gave evidence that hospital effluents have an impact on the biomass in activated sludge basins which may result in physical, biochemical and biological alterations (Stalder & al, 2013).

Moreover there was an increase in the number of bearing-cassettes integrons encoding resistances to certain antibiotics.

6.4.4 Summary and policy pointer

Summary:

The process efficiency to eliminate compounds is dependent on both the applied treatment concepts and the intrinsically linked properties of the compounds: chemical structure, sorption capacity, and biodegradability.

Feeding a biological basin with hospital effluent must have consequences on the bacterial populations found there. As part of noPills, different approaches have been undertaken to characterize these potential changes in all studied systems.

The cross-analysis of the results leads to the conclusion that the hospital effluents impact the conventional activated sludge bacterial populations by inducing different alterations (Stalder & al, 2013):

- Physically: erosion of flocs
- Biochemically: increased production of extracellular polymeric substances (EPS)
- Biologically: a change in the population with the introduction of Pseudomonas spp., known for its potential to produce EPS
- As a result this poses a potential risk: the impact of hospital effluents on bacterial populations was by quantification of resistance integrons. The relative abundance of class 1 RIs (Resistance Integrons) in the hospital effluent (HE) was higher than that in the urban effluent (UE).

Policy pointers:

The need of additional treatment efforts should be assessed if significant inputs of hospital effluents occur in centralized WWTPs.

6.5 Removal of pharmaceuticals from wastewater by ferrate treatment: a case study in Scotland and Germany

The potential role of ferrate for the removal of micropollutants was evaluated within a recent review paper (Jiang, 2013). Within the noPILLS partnership a mobile ferrate pilot plant was constructed and the process tested under identical process conditions both in the UK and at the Emschergenossenschaft's WWTP Emschermündung "technikum" [a test treatment plant]. This allowed comparative studies on ferrate treatment in laboratory conditions in a series of trials with actual municipal waste water and also waste water from the HWWTP Marienhospital Gelsenkirchen. The latter trials were conducted in Germany from September to November 2014, and samples were analysed in parallel in both partner labs.

6.5.1 Objectives

Glasgow Caledonian University contributed to the previous PILLS project by assessing ferrate performance in the removal of pharmaceutical residues in wastewater. The results revealed that ferrate could be an excellent alternative to other advanced oxidation processes. The noPILLS pilot scale trials were conducted in order to validate the laboratory based results, to evaluate potential full-scale use of ferrate to treat pharmaceuticals from wastewater and to define optimal operating conditions.

Ferrate technology is innovative in the context of traditional oxidation and coagulation for both drinking water and waste water treatment. The need for intensive pre-treatment of waste water prior to advanced treatment means that this technology can be more suitable for waste water treatment. Ferrate also has the additional potential advantage that it not only oxidises organic substances but can also effect the removal of particles due to physico-chemical reactions. This means that it is also possible to transfer a larger part of substances into the solid phase so that they might be removed, even if not destroyed, from the waste water. The specific objectives of this research were:

- To determine the optimal operating conditions (e.g., ferrate dose) in order to maximise the micro pollutants (pharmaceuticals) removal from various wastewaters.
- To assess routine treated wastewater quality parameters, e.g. SS, COD, PO4-P, UV abs, etc.
- To conduct toxicity assessment for the selected wastewater samples.

6.5.2 Wastewater Sources and Sampling

At Emschergenossenschaft, municipal wastewater was collected from various sampling points and treated in the ferrate pilot plant. Additionally, hospital wastewater was collected at the HWWTP Marienhospital Gelsenkirchen and transported to the Emschergenossenschaft Technikum to be treated by the ferrate pilot plant.

At GCU, wastewater samples were collected after the secondary sedimentation stage of a municipal WWTP employing conventional activated sludge technology.

6.5.3 Results achieved from the studies at the Emschergenossenschaft

The micropollutants removal was dependent on the considered compounds. Some substances were completely removed (below the detection limit). Most micropollutants can be removed except for iomeprol and diatrizoate; in comparison with others, these two compounds have high concentrations in the raw hospital effluent, causing difficulties to be treated by ferrate alone. For some compounds the removal rate was controlled by the applied ferrate dose. For the treatment of municipal wastewater, a ferrate dose of 4 mg/L is demonstrated to achieve the best performance. For the tertiary treatment, 2 mg/L of ferrate was efficient to reduce most micropollutants to very low level. Surprisingly, higher doses (i.e. 13 mg/L ferric dose) were not effective to achieve the acceptable performance.

As well as removing various micropollutants, ferrate simultaneously performed general waste water treatment tasks. The quality of treated domestic wastewater can be improved by reducing COD and suspended solids if the secondary effluent was further treated by ferrate at a dose of 2 mg/L (as Fe). Similarly, the superior performance of ferrate was observed in treating hospital wastewater; dosing 2-3 mg/L ferrate into the MBR effluent outperformed that of MBR with ozonation, especially for the COD and phosphate reduction.

6.5.4 Results achieved from the studies at Glasgow Caledonian University

General wastewater parameters like COD, phosphate, UV254, Vis. Abs.400 and NO2-N in the secondary sedimentation effluent were further reduced by a ferrate dose of 2 mg/L, while suspended solids concentration increased, suggesting the settling performance was not as good as that observed elsewhere. Analytical results from the GCU laboratory were not available at the time of writing.

Luminometer tests (BioFix Lumi-10) indicated that ferrate treatment satisfied the validation requirements in that they demonstrated that none of the test samples (both ferrate treated and non-treated) had inhibitory effect on the bacteria growth, suggesting that dosing ferrate into the secondary effluent for the removal of micropollutants would not cause any toxic effect to aquatic microorganisms.

6.5.5 Summary and policy pointer

Ferrate can effectively reduce concentrations of most studied pharmaceutical substances which were present in both domestic raw sewage or effluent and hospital wastewater or treated effluents. Ferrate simultaneously reduced COD, phosphate, colour and UV abs when in the degradation of micro pollutants, suggesting that it is likely the ferrate can be used in large scale wastewater treatment practice.

Policy pointers:

Additional investigations at pilot-scale are needed to assess the full-scale applicability of ferrate technology for advanced wastewater treatment.

6.6 Lessons learned: Experiences from wastewater treatment at hospitals

Based on the long-term operation of a full-scale hospital wastewater treatment plant and based on pilot-scale investigations on novel advanced wastewater treatment techniques the following conclusions can be drawn:

- Decentralized treatment of hospital effluents is technically feasible.
- The general composition of hospital effluent in terms of temperature and nutrient content supports the mechanical-biological treatment according to the activated sludge process.
- Experiences from municipal wastewater treatment can be transferred.
- Given appropriate boundary conditions a good treatment efficiency at decentralized hospital wastewater treatment plant is possible – especially for the biochemical processes like MBR
- The majority of micropollutant's load can be removed and a disinfected final effluent can be provided by MBR treating hospital effluents.
- Energy demand for decentralized hospital wastewater treatment is higher than for centralized wastewater treatment.
- Operational efforts (staff, resources) are comparable to centralized WWTPs.
- Source separation of different wastewater streams like rain water, domestic wastewater and effluents of specific hospital departments supports the design and operation of decentralized treatment of hospital effluents.
- A reliable and sustainable residual management (sludge and screenings) can be established at decentralizes HWWTPs.
- An appropriate design of the HWWTP and its building is able to cope with the legal requirements regarding noise and odour emissions.
- Depending on the boundary conditions decentralized treatment and source separation measures can be economically feasible.
- The cooperation with local wastewater service providers (e.g. water boards) allows a proper implementation and a reliable operation of the decentralized HWWTPs.
- A proper waste management at the hospital is the prerequisite for a reliable operation of the decentralized HWWTP.
- The optimized waste management at the hospitals can be developed in cooperation with the operator of the decentralized HWWTP and is economically feasible.

- The innovative and sustainable approach of decentralized wastewater management at hospitals results in a positive public perception for the hospital and the operator of the decentralized HWWTP.
- New advanced treatment approaches have the potential to increase energy and resource efficiency of advanced treatment in decentralized and centralized waste water treatment.
- Hospital effluents may have an impact on the performance of centralized WWTPs.

Policy pointers:

Decentralized hospital wastewater treatment plants equipped with MBR technology are reliable in operation and allow for a significantly improved wastewater quality in terms of organics, nutrient, micropollutants and bacteria. Further evaluation in terms of costs and cost-efficiency benefit is required.

7 Tools for targeted communication campaigns

The dissemination and exploitation of the noPILLS project findings and topics to the public was of high importance for noPILLS. Sharing of complex specialist information in a simplified and informative manner was amongst the main aims of the project as it could affect the public's future behaviours and attitudes towards medicine consumption and disposal. This Chapter describes activities and tools that were developed and tried in Germany and Scotland.

7.1 Germany

In the Dülmen case study, community-wide communication campaigns as well as communication campaigns for the target groups medical and pharmaceutical professionals were conducted (see also chapter 3).

Target group	Activities and tools
Community-wide	• Projects in Schools and youth care facilities • Citizens' forum as opening event and closing ceremony of the case study • Citizen meetings / information campaigns on the marketplace • Flyer in the trash calendar to inform about proper ways to dispose of leftover medicines • Mini Book on medicines in waters • Brochures to raise awareness of the issue • Guiding tours on the local sewage treatment plant (with the aim to demonstrate the limits of treatment technology to eliminate medicines residues in wastewater. • Running event (in cooperation with sports clubs, the city and the local radio); running along the rivers and the local sewage treatment plant; Accompanied with information stands for information on the subject) • Website with an animated presentation, movies, variety of information on the topic • Animated movies on YouTube • Press events (ground-breaking ceremony and start of operation of the new powdered activated carbon step at the local sewage treatment plant) • Press articles, radio reports and TV reports on the various awareness campaign activities
Medical and pharmaceutical professionals	• Working meeting with doctors, pharmacists and medical staff • Information sessions • Certified continuing education seminar for medical and pharmaceutical professionals • Presentations and lectures by experts on the issue
GPs / Population	• Two-week campaign "GPs' campaign" • Posters, flyer and brochures
Pharma-cists / Population	• Two-week campaign "spring cleaning in the medicine chest" • Kit for pharmacies: Supporting pharmacies receive a kit consisting of a poster, beach flag, information flyers, give-aways, etc.

Table 7.1: List of activities and tools for community-wide communication campaigns in the Dülmen case study

In the 'case study Dülmen', at least one-third of the surveyed households were aware of the various activities and tools. More than half of the respondents were aware of the individual actions such as the running event, which was realized in cooperation with two sports clubs in Dülmen, or the two-week campaign "spring cleaning in the medicine chest".

The information materials (such as brochure, leaflets, flyer and posters) were viewed positively. About 53 % of the respondents knew of the flyer about a pharmaceutical 'spring clean'; 43 % of the respondents took notice of the posters in GPs' offices and pharmacies. About 77 % of the respondents evaluated the actions, events and materials to be informative or very informative.

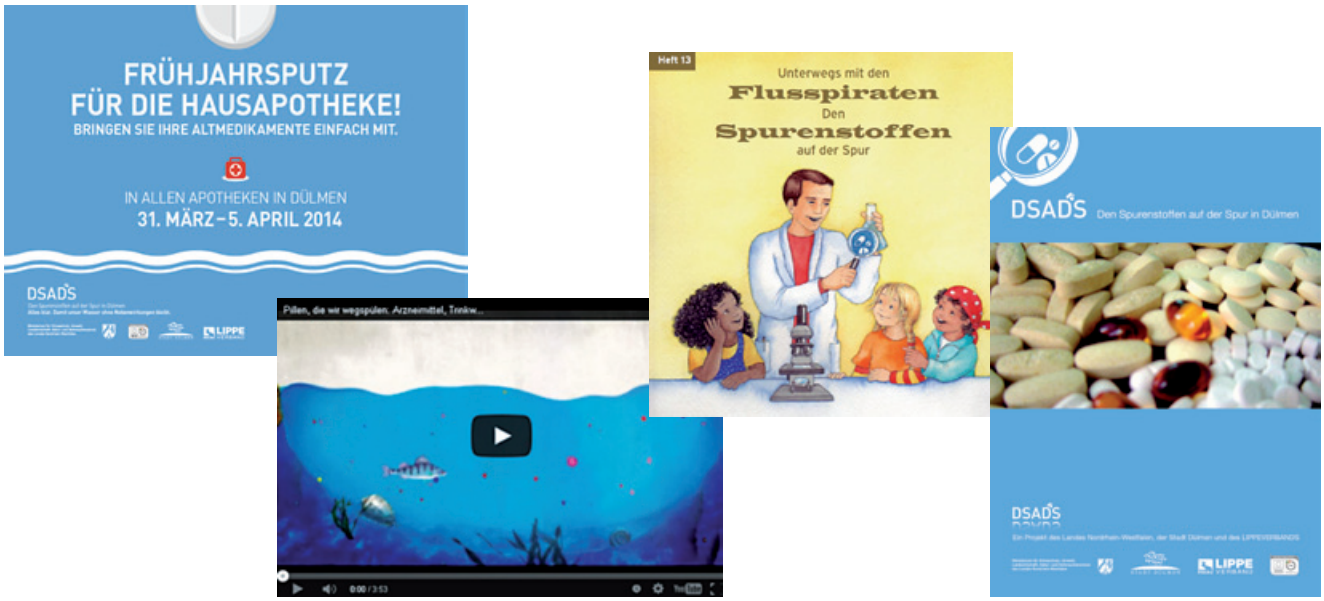


Figure 7.1: Examples of tools for community-wide communication campaigns in the 'case study Dülmen' (clockwise from top left: poster for the two-week campaign spring cleaning in the medicine chest; mini book on medicines in waters; animated movie on medicines in waters; Dülmen brochure)

On the other hand a part of the citizens remained unaware. About 30 % of the surveyed households did not see any information materials, 19% didn't hear of the actions and 9 % were unaware of the materials or information campaigns. This was particularly true for those between age 46 and 65.

The most effective media for the community-wide communication of awareness activities was found to be the local newspaper, followed by the local radio and the regional TV. The most effective tools were the flyer in the trash calendar, followed by the leaflet on the topic designed by school students and posters in doctors' offices and pharmacies.

A lesson from the Dülmen case study is that directly addressing doctors and pharmacists is important in order to raise awareness of this target group and to get them involved in the targeted awareness campaigns for patients and consumers.

Summary:

- Conventional communication media, such as the local newspaper, the local radio and the regional TV are effective for the community-wide communication of awareness activities.
- Posters in doctors' offices and in pharmacies are important tools for the communication of the issue to patients and consumers.
- Doctors and pharmacists should be addressed directly and should be involved in the targeted awareness campaigns for patients and consumers.

Policy pointers:

- Simple but professionally designed posters in pharmacies and doctors' surgeries can be very effective for awareness raising of patients and consumers on the issue. The same applies to flyer and leaflets with appropriate information on the issue as supplement to public brochures or corresponding reports in local newspapers, local radios and regional TV.

7.2 Scotland

In Scotland two modern communication tools were developed that are described below:

- 3D Virtual Reality system
- Game Jam

7.2.1 3D Virtual reality system

Previous work at GCU showed that to offer information in a user-friendly way by data visualisation can help to make data easier understandable and also highlight major points. At the same time, data visualisation can be combined with virtual reality elements and, again, previous work at GCU showed that this can improve 'buy-in' into the information offered, i.e. increase (intended) engagement with the data and eventually also promote intended behaviour. The noPILLS project sought to investigate the transfer of this technique, which had previously been applied primarily in the automotive/transport sector, to the theme of pharmaceutical micropollution in water as an awareness raising tool: conveying complex information on water pollution, most likely in a context (pharmaceuticals) many members of the public have not previously been exposed to, without overloading the average and non-specialist user with unnecessary terminology and information. As such, a 3D Virtual Reality map model of a selected region (the White Cart River) was developed as a tool to provide visualisation of environmental data at Points of Interest (POI). The data were in turn visualised and allocated in the 3D map offering a clear overview of the different concentrations and patterns arising along the river (Figure 7.2)

The 3D application can be updated dynamically and retain a track record of values that present long-term changes. Depending on the response of the public to this tool – aimed at increasing awareness through local outreach

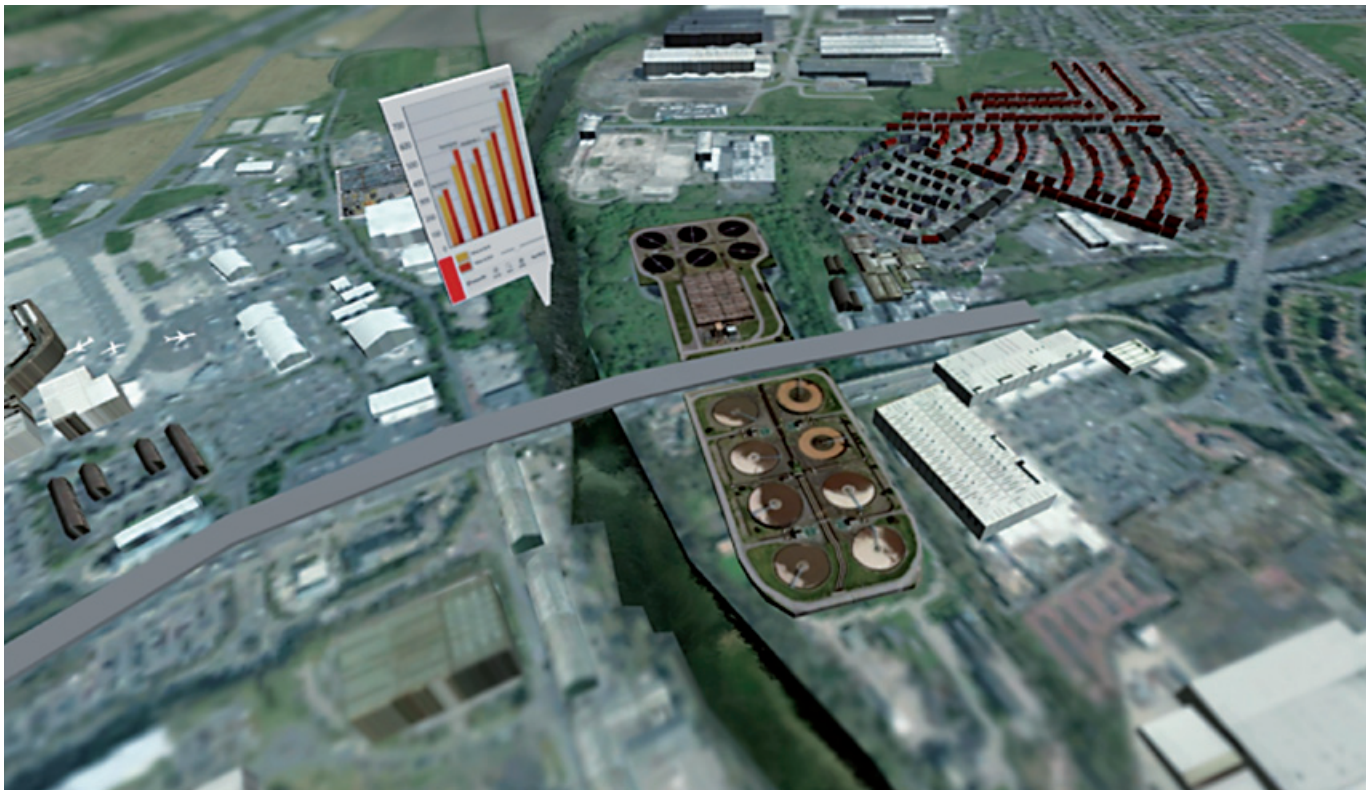


Figure 7.2: Screenshot of 3D fly-through visualisation

- behaviour change initiatives regarding, e.g. the disposal of medication in the near future, could be supported by clearly visible pollutant levels in the 3D data visualisation.

The 3D/VR application offers to the public the ability to fly over the length of the river and visit Points Of Interest (POIs). Detailed 3D visualisation of landmarks in close proximity to the river such as the airport, shopping malls, hospitals, stadiums and parks amongst other, are offering a direct mental-linking to the impact of the population's actions to their everyday activities and lifestyle. This is evident, especially wherever the concentration of substances in the water is at elevated levels, in close proximity to the aforementioned POIs. The data visualisation, in addition to typical graphs, offers different interface presentations based on symbolic representations and colour coding so as to be easily understandable by different age groups, genders, backgrounds and cultures. In order to achieve better usability of the system we opted to utilise gesture recognition for the data interaction and the fly-through navigation.

The system is fully functional in a typical non-3D computer monitor, TV or projector, and can be manipulated with a keyboard or mouse in the absence of a gesture recognition device such as Xbox Kinect. It is also accessible online. Ongoing trials in the Virtual Reality and Simulation Laboratory (VRS Lab) in GCU have generated an enthusiastic and positive response from the public and a series of major events will host the system for public display.

7.2.2 Game Jam

For enhanced dissemination to the younger population of the public, GCU worked with game developers who targeted the issue of medicine disposal and resultant environmental effect via a serious-game approach: in July 2014, GCU hosted the noPILLS game jam. A game jam is an event where designers, developers and artists come together to create games and other digital products in 48 hours. While most game jams are designed for entertainment, there has been an emergence of game jams for a more serious purpose, such as the recent game jam hosted by Cancer Research UK, the Health Game Jam or Jamming 4 Small Change.

The noPILLS project is a complex area and applying a serious games approach offers an effective method to help raise awareness about the

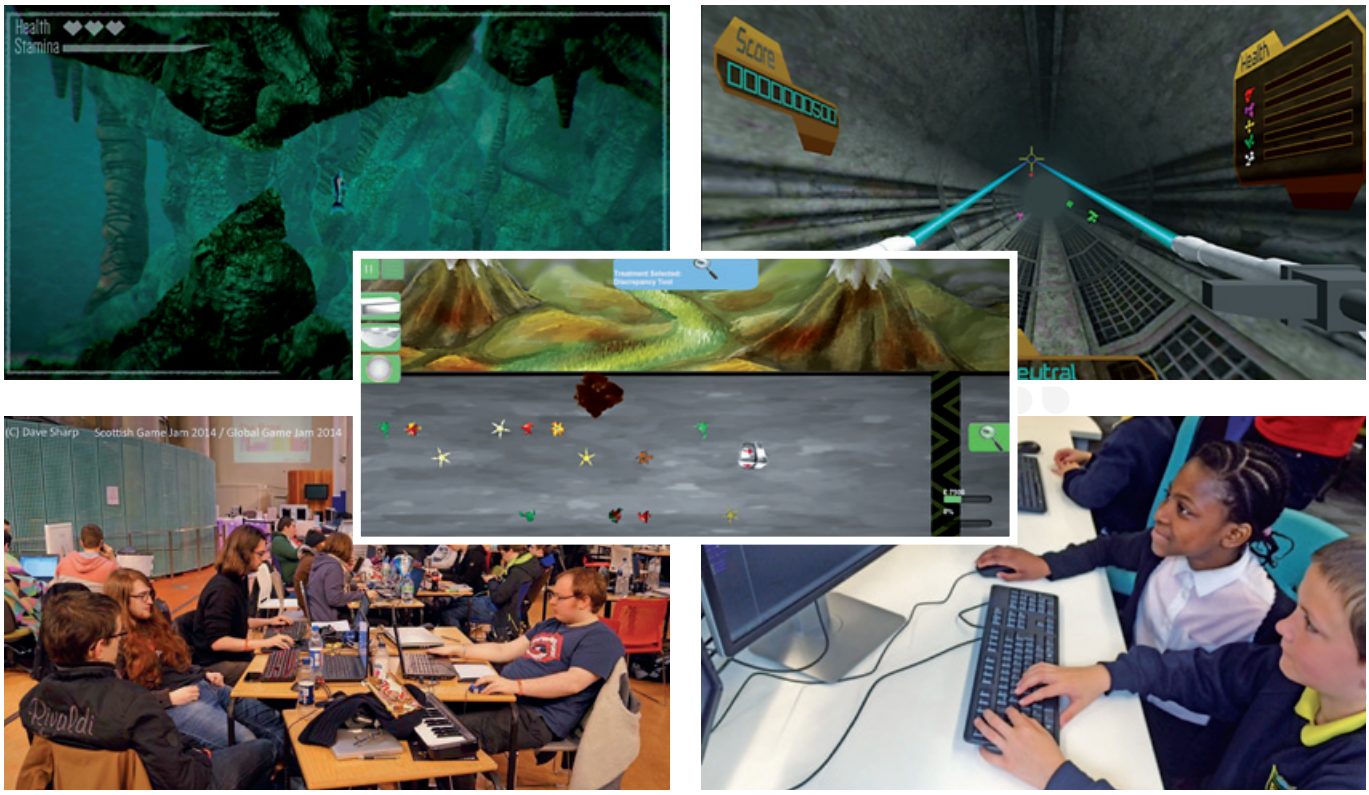


Figure 7.3: Examples of game jam outputs (Clockwise from top left: Pollution" screenshot; "Purity" screenshot (centre); "Sewer Sweeper" screenshot; game jam with primary school children; game jam setting)

project. Serious games have the potential to engage large sectors of the population to increase the awareness of important environmental and societal issues. The typical game audience would otherwise not be motivated to explore such issues. Serious games are computer and video games that are designed to entertain users, however, their main purpose is to educate. Commercial off-the shelf games can be used, but often, it is better to create bespoke products, because accurate, more authentic content is sometimes required, as is the creative input of 'gamers'. Given the nature of the noPILLS topic, which is not only complex but also one that most gamers have not been exposed to before, one of the main observations made was that gamers can translate this complex and 'obscure' concept and produce game storyboards for a number of target audiences (i.e. social gamers, educational gamers, primary school age children) in a very short time and with a high degree of enthusiasm. These games then need to be developed into fully functional products and their potential for awareness raising tested. However, our initial observations would indicate that early involvement of gamers, rather than topic specialists, in games development is a promising route. A further game jam for young children was held in May 2015 as a continuation of this line of investigation.

The noPILLS games jam (Figure 7.3) produced a number of games out of which, three have been commissioned by the noPILLS team to be used for dissemination:

- The first game, Sewer Sweeper, is a first-person on rails shooter set in pipes beneath towns and cities. The aim of the game is to clean away micro particles of pharmaceuticals discarded by people in the water system. The game uses different sources of pollutants as targets, which the player learns about as they progress through the game.

- The concept for the second game, Purity, is that technicians, operators and the general public may be unaware of the effects of pharmaceutical pollution. The player has to reduce their environmental impact by adapting to changing situations in a sewage treatment scenario, and in the process acquires knowledge and situational awareness.

- The third game is based on a fish's journey in a polluted river. The player needs to avoid pollutants and in the process learns about pharmaceutical residues originating from sewer outfalls and potential abatement based on (disposal) behaviour. This game is primarily aimed at younger children (primary school age).

These games will be released to the general public and targeted audiences (e.g. water company staff or students), respectively, and user feedback to these serious games monitored and evaluated in a new research project that will continue this initial work for three years from 2015-2018.

Summary:

Modern media products such as 3D visualization and computer games were identified as potential tools to increase awareness of environmental pollution. Initial observations obtained from programmer and user feedback is positive, and will be followed up – beyond noPILLS – with detailed monitoring of user feedback on the products.

Policy pointers:

Local outreach and wider awareness raising campaigns on thematically complex topics such as pharmaceutical residues in water may benefit from the use of modern communication tools such as 3D visualization and computer games. Further work is needed to verify and quantify the efficacy of these tools.

8 Conclusions and Policy pointers

This chapter briefly summarises the activities undertaken in the noPILLS project, conclusions taken from these activities and recommendations for intervention actions ("policy pointers").

8.1 Conclusions

Chapter 2, Formulating understanding of actors and processes: identification of levers for intervention, describes the whole medicinal product chain from design of pharmaceuticals through to licencing, prescribing, dispensing, use, disposal, and ingress and fate in the environment. Important processes, actors, levers for intervention, and international and regional differences are described especially for those phases of the medicinal product chain that involve users of pharmaceuticals. This review, whilst concentrating on the situation in the Netherlands, provides important generic policy pointers for consideration outwith their geographical context, and informed the engagement case studies conducted in the noPILLS project.

The conclusions from this chapter are that in the medicinal product chain many actors are active, all taking decisions from their own specific interest, based on regulations specifically made for the partial process they are involved in. These decisions may be health driven, society driven, economy driven, environment driven, etc. By placing all the partial processes and the interests of the different actors in one scheme, optimization possibilities for the medicinal product chain become clear, resulting in levers to use to optimize the process for society.

In more detail, purchasing choices by or for a patient are influenced by a chain of actors that are mutually interdependent and they influence the processes of medicine use and disposal. First, the pharmaceutical industry and marketing regulation authorities affect which medicinal products are available to choose from. Additionally, the distribution channel (OTC or prescription) affects availability and subsequent purchase and disposal of medicines. Next to the health problem that the patients have, physicians are known to make different choices in similar clinical situations. Also the reimbursement policy of the insurer affects which medicinal product is used. Changes by one or more of these actors will affect whether the medicine needs to be disposed of. Patients have shown to be willing to conduct more effort to dispose of medicine in an environmental friendly way if they are made aware of the problem, but this analysis also shows that also on the institutional level choices can be made to reduce the influx of potentially harmful compounds in the environment.

Chapter 3, Pharmaceuticals in sewage systems and surface waters – status quo, summarises new findings and insights relating to the occurrence of pharmaceuticals in the environment, as were apparent from various sampling campaigns in rivers, wastewater treatment plants and sewage sludges in the UK, France, Luxembourg and Germany.

The chapter concludes that:

- Pharmaceuticals are ubiquitously present in the receiving aquatic environment and a clear increase in concentrations was observed after sewage effluent enters rivers. Some pharmaceuticals, including macrolide antibiotics, were present in toxicologically relevant concentrations. The available environmental dilution is an important factor in the risk ensuing from effluent concentrations; especially where multiple discharges enter the same surface water the dilution capacity can be less than suggested by flow volumes;
- Pharmaceuticals are partly sorbed to sludge by hydrophobic type interactions, but mainly by electrostatic interactions. Stabilisation processes during sludge treatment could modify these interactions depending on the process. Molecules are then available and can reach water bodies;
- Conventional WWTP are effective in reducing ecotoxicity levels but some toxicity remains;
- Over 20 % of Scottish river samples were acutely toxic to aquatic organisms, indicating high pollution levels. However, it must be noted that it is not certain that the toxicity is due to pharmaceutical content alone;
- Sewers may contain a resistant bacteria load. The relative abundance of resistant bacteria in hospital effluents was higher than in an urban effluents;
- The quantification of integrons and relative abundance could be a method to evaluate an overall resistance before a specific identification with molecular techniques.

Chapter 4, Reducing the pharmaceutical load at source: engaging society about pharmaceutical consumption and disposal, describes engagement-research activities, primarily with members of the general public in three case-study countries (France, Germany and Scotland) but also, to a degree with some key stakeholders in two partner countries: Germany and France. Key themes addressed in each activity are (patterns associated with) consumption of prescribed and over-the-counter (OTC) medicines, disposal, attitudes to stakeholders, attitudes to health, and awareness of (associated) environmental issues. As different methodologies were applied specific to the respective research objectives, results are not directly comparable. However, the activities generally sought to develop understanding of the societal context of medicine use and to identify 'policy pointers' for potential levers to engender behaviour change or to raise levels of awareness.

The chapter concludes that members of the public, patients and healthcare professionals are generally receptive to the idea of reducing the environmental burden arising from medicinal residues in the environment. However, it would appear that this underlying 'appetite' for an agenda that seeks to reduce medicinal input is hindered by a lack of information, engagement between patients and healthcare professionals, and consistent messages and processes.

Using a range of methodologies, the three case studies indicate a clear sense that members of the public, in particular have a considered view on the (over)use of medication. There is a consistent message that they would wish to have more information on appropriate use and disposal, but that this needs to be in an accessible form. Equally there is a more general view on the lack of information about appropriate disposal mechanisms; again a common view is held that the existing mechanisms for this are inconsistent and more importantly appear to lack clarity. And yet there is a great desire by members of the public in particular to 'do the right thing'.

Chapter 5, Reducing emissions of pharmaceutical residues to surface waters by implementing measures of source segregation, assesses the feasibility and efficiency of source segregation measures on hospital level especially for specific substances like cytostatics or contrast media that, due to the fact that an important amount of substances is administered to ambulant hospital patients or to patients outside of hospitals, may be released into the environment also outside the confines of the hospital. In this sense, the chapter goes beyond separation of hospital wastewaters and concentrates instead on separation of specifically important pharmaceutical substances on the patient-level. Campaigns using urine collection bags were conducted in two hospitals in Luxembourg and Germany.

The chapter concludes that:

- It is possible to include procedures needed for separate collection of urine in the routine treatment of patients in radiology departments;
- The separate collection and disposal of urine of ambulant patients (Luxembourg) and of all patients (Germany) resulted in a detectable reduction of emissions at hospital and catchment level;
- Key for the efficiency of a separation campaigns is the active involvement of medical staff (for the motivation and engagement of patients). There is also a clear need to inform the medical staff about the environmental effects of pharmaceutical residues in the environment;
- The estimated additional amount of time to implement separate collection at the level of radiology departments is 5 to 10 minutes per patient and consultation.

Chapter 6, Occurrence and removal of pharmaceuticals by advanced treatment of hospital wastewater, describes occurrence of pharmaceuticals in hospital wastewaters and evaluation of selected hospital wastewater treatment options.

Full-scale evaluation of techniques included membrane bioreactor (MBR), powdered activated carbon (PAC) and ozonation; pilot-scale techniques included advanced oxidation with ferrate, MBR, and ozonation; and small-scale techniques concentrated on biological activated carbon (BAC). These complementary approaches involved long-term monitoring of hospital wastewater and operation of the various wastewater treatment technologies at full-scale hospital WWTP, and short term application of the novel technological approaches at pilot- and small-scale.

The chapter concludes that:

- Iodinated X-ray contrast media (ICM) represent the highest load of micropollutants in hospital effluents (by an order of magnitude. The main load of ICM in hospitals is caused by a few hospital departments (radiology, cardiology);
- Experiences from municipal wastewater treatment can be transferred to hospital wastewater treatment, and adherence to established design criteria for municipal wastewater treatment prevents the inhibition of biochemical wastewater treatment processes by hospital effluents;
- MBR technology improves treatment efficiency regarding micropollutants in comparison to centralised municipal wastewater treatment, and the majority of micropollutant load can be removed;

- Energy demand for decentralised hospital wastewater treatment is higher than for centralised wastewater treatment, but operational efforts (staff, resources) are comparable to centralised WWTPs;
- Source separation of different wastewater streams like rain water, domestic wastewater and effluents of specific hospital departments supports the design and operation of decentralised treatment of hospital effluents. Depending on the boundary conditions, decentralised treatment in combination with source separation measures can be economically viable;
- Proper waste management at the hospital is a prerequisite for reliable operation of decentralised HWWTP;
- The innovative and sustainable approach of decentralised wastewater management at the case study hospital resulted in positive public perception for the hospital and the operator of the decentralised HWWTP;
- Novel advanced treatment approaches have the potential to increase energy and resource efficiency of tertiary treatment in decentralised and centralised waste water treatment. In particular moving bed biofilm reactor and ferrate treatment demonstrated increased pharmaceuticals removal and simultaneous reduction in COD, phosphate, colour and UV abs, respectively, from sewage and hospital wastewater, suggesting that these technologies have potential for uptake in wastewater treatment practice.

Chapter 7, Tools for targeted communication campaigns, takes cognisance of the fact that dissemination and sharing of complex specialist information in a simplified and informative manner can affect people's attitudes and behaviours towards medicine consumption and disposal. This Chapter describes activities and tools that were developed and tried in Germany and Scotland, which were targeted at whole-community level (the town of Dülmen) and a specific segment of society: (younger) people engaged in modern media (computer gaming and online information gathering).

The chapter concludes, respectively, that:

- Conventional communication media, such as local newspaper, radio and TV were effective for community-wide communication of awareness activities;
- Posters in doctors' practices and pharmacies were important tools for communication with patients and consumers;
- Doctors and pharmacists should be addressed directly and should be involved in targeted awareness campaigns for patients and consumers.
- Modern media products such as 3D visualization and computer games are potential tools to increase awareness of environmental pollution;
- Initial observations obtained from programmers and user feedback was positive but requires further research and detailed monitoring of user feedback.

8.2 Policy pointers

The noPILLS project partners' intention for this report, as mentioned in Chapter 1, is to share their results and experience and thus contribute to the European discussion and subsequent decision making processes. The partners feel that their approach of interdisciplinary evaluation of transnational case studies provides a unique insight into practical aspects of intervention measures.

In order to integrate into the ongoing discussion in Europe, which is largely following the structure of the BioIS (2013) study on the environmental risks of medicinal products, we present our recommendations for intervention implementation cross-referenced against seven of the nine non-legislative "factors of influence and possible solutions" BioIS themes, keeping in mind that some results could span two or more of these themes:

Theme 2: Developing and harmonising the implementation of collection schemes for unused medicinal products (noPILLS report Chapter 3)

Further research and development is recommended to optimise and harmonise the practical operation of pharmaceutical take-back schemes.

As returning medicines to the pharmacy may increase the time medicines are stored at home, suggestions for safe storage of waste medicines may help to

address any concerns the public may have. There is existing goodwill around the safe and secure storage of medicines, which can be built upon: People are familiar with the concept of correct and incorrect disposal (e.g. through experience with recycling collections) and are in general prepared to separate their waste and dispose of it correctly, particularly so when considering safety (for people) is an issue. This might be further encouraged;

Clear, consistent information on the practice and rationale of disposal facilities may encourage optimised disposal behaviour. As disposal via toilet or sink still accounts for a considerable amount of pharmaceuticals, a worthwhile reduction could still be achieved by addressing this behaviour;

Access to repeat prescriptions may lead to stocking up on medicines and harmonised return mechanisms ("medicines amnesty") may lead to increased uptake (by patients and relatives).

Theme 3: Developing source separation measures (noPILLS report Chapter 5) and wastewater treatments (noPILLS report Chapter 6)

- Separate collection and disposal of urine of hospital radiology patients can significantly reduce substance flows of Iodinated X-ray contrast media (ICM) to surface waters;
- Separation at source taking the example of urine separation of ICM on hospital level can even work efficiently under difficult boundary conditions (e.g. patients with different native languages and cultural background);
- Results can be transferred to other substances administered in high amounts in hospitals and having similar properties as ICM (excretion path, persistence etc.);
- Measures of segregation like separate collection of urine also offer possibilities to recover specific substances;
- Hospitals are a large source of contrast agents: separate collection (capture) of specific wastewater streams at hospitals is possible and economically feasible;
- Hospital wastewater can be collected prior to dilution in the sewer system;
- Design criteria from municipal wastewater treatment can be transferred to hospital waste water treatment;
- Decentralised treatment of hospital effluents on-site can be reliable;
- MBR treatment efficiency at hospitals can be comparable to the efficiency of advanced tertiary treatment at municipal WWTPs;
- Sanitised effluent can be obtained by ultrafiltration in MBR treatment.

Theme 4: Actively involving public society and professionals through information and education (noPILLS report Chapter 2, Chapter 3 and Chapter 6)

Medicine use

- There would appear to be an appetite, by members of the general public, as potential patients, for an agenda that seeks to reduce medicinal input – policy might address this by encouraging alternative forms of appropriate therapy;
- People's OTC purchasing decisions are influenced by a complex set of factors. This 'diffuse information' source does not offer a single straightforward point of intervention for the reduction of OTC consumption but rather suggests a multi-pronged approach;
- Positive lifestyle choices such as diet and exercise should continue to be promoted both as preventative and as curative health interventions, whilst barriers to implementing these might be explored and addressed;
- Appropriate pack sizes may reduce medicine wastage. Issue of repeat prescriptions, change of therapy and condition of patient (with due consideration!) may also be appropriate moments to reinforce a correct disposal message or offer a collection service.

Potential roles for Stakeholders

- The Medicinal product chain analysis clearly demonstrates that many stakeholders in the medicinal product chain have options to reduce medicinal waste.

- People feel a range of stakeholders could contribute to the reduction of pharmaceutical consumption and are also prepared to accept that they themselves have a role to play;

There are also clear indications that over the longer term substantial engagement with a range of stakeholder groups may generate new approaches to prescribing and acquisition of medicines;

- Pharmacists are seen as key group to inform consumers on environmental consequences and proper way of disposal.

Environmental awareness issues

- Information, education and publicity would be welcomed by members of the public, both on disposal advice and on the wider issue of pharmaceuticals in the environment;

- Simple but professionally designed posters in pharmacies and doctors' surgeries can be very effective for awareness raising of patients and consumers on the issue. The same applies to flyer and leaflets with appropriate information on the issue as supplement to public brochures or corresponding reports in local newspapers, local radios and regional TV.

- Local outreach and wider awareness raising campaigns on thematically complex topics such as pharmaceutical residues in water may benefit from the use of modern communication tools such as 3D visualization and computer games. Further work is needed to verify and quantify the efficacy of these tools.

Theme 5: Prioritising and monitoring molecules and/or environmental compartments of concern (noPILLS report Chapter 3, as well as the whole previous PILLS report)

- Monitoring of raw sewage discharges, especially those from CSO in wet weather situations, is recommended. Similarly, non-WWTP sources may contribute significantly to pharmaceutical loads in the aquatic environment. Further research is needed to verify this and to determine the relevance of other sources, as actions to upgrade WWTP may not be sufficient to protect the environment;

- Current levels of several pharmaceuticals, including macrolide antibiotics, in WWTP effluents may pose toxic situations in surface waters unless significant environmental dilution is available. Some of the macrolide antibiotics on the 'Watch list' may be present in sufficient quantities to pose an actual environmental risk. More extensive monitoring of these compounds is recommended;

- Risk assessments should where possible consider realistic available dilution and take account of multiple inputs as cumulative loads;

- Potential contamination of sludge during biological treatment, and stability of sorption, has to be considered in the overall balance of removal and in decision making on the use of sludge in land application;

- Research into the pharmaceutical contribution to toxic effects in surface waters is recommended;

- Research on ecotoxicological tests has to be improved to define the most relevant environmental impact(s) for monitoring;

- It is recommended that ecotoxicity of whole effluent should be considered as a discharge parameter in licensing, in order to account for full complexity of the mixture of whole effluent and surface water bodies;

- The fight against antibiotic resistance requires a range of approaches, which could include:
  - standardization of quantification methods,
  - definition of indicators to monitor ARB – such as integrons used in this study,
  - definition of a methodology for risk assessment,
  - evaluation of gene transfers in anthropic systems;

- Control of resistant bacteria at source could play a role in maintaining effectiveness of antibiotic treatments;

- Fundamental research on resistant bacteria and gene transfer in sewage effluents is recommended.

Theme 6: Consolidating existing knowledge, ensuring transparency and facilitating access to information (noPILLS project overall as a knowledge exchange activity)

- The medicinal product chain shows that all actors involved in the medicinal process in principle could contribute to the reduction of medicinal waste.
- The indication is that individuals would appreciate more (easily accessible) information about alternatives but also more widely about appropriate related behaviours for example disposal;
- Simple but professionally designed posters in pharmacies and doctors' surgeries can be very effective for awareness raising of patients and consumers on the issue. The same applies to flyer and leaflets with appropriate information on the issue as supplement to public brochures or corresponding reports in local newspapers, local radios and regional TV;
- Local outreach and wider awareness raising campaigns on thematically complex topics such as pharmaceutical residues in water may benefit from the use of modern communication tools such as 3D visualization and computer games. Further work is needed to verify and quantify the efficacy of these tools;
- Prescribing and self-medication is influenced by many factors other than therapeutic need. Marketing, continuing education and professional literature may be useful media to influence behaviour to drive optimal therapeutic and environmental outcomes;
- Including environmental information and appropriate disposal practices in information exchange during prescribing/delivering and on Patient Information Leaflet (PIL) is recommended, as disposal information in the PIL alone may not be read and alternative information sources may need to be provided;
- There are many misconceptions about what constitutes 'safe' disposal of medicine (for people vs for the environment) and sustained information dissemination is needed to address this. The 'waste disposal' message on pharmaceuticals may be usefully included in local authority recycling information;
- Peer education may be an effective way to encourage behaviour change around disposal.

Theme 8: Implementing incentive economic instruments (noPills report Chapter 2 and 4)

- People have little or no understanding of the cost that would be involved in advanced wastewater treatment and may be more prepared to change disposal behaviour if they were;
- Appropriate pack sizes may reduce medicine wastage;
- Insurers could be involved in discussion about reimbursement of environmentally friendly alternatives such as non-medicine treatments or 'greener' medicines;
- Although price is a factor in purchasing decisions, its influence is ambiguous: a high price could make a product either more or less attractive to buy. Price control might not necessarily be a useful driver for behaviour change with regards to OTC medicine purchasing and hence might be a problematic 'intervention point' for consumers (although price maybe more important for other stakeholders).

Theme 9: Developing the knowledge base through fostering of research activities (noPILLS project overall as a joint research project with a focus on multi-disciplinary work)

- It is recommended to undertake a thorough exploration of perceptions (see Box 8.1) at the outset of inter- or multidisciplinary projects to ensure all participants and stakeholders are engaged as the project progresses and that such reflections continue throughout the project.

  The noPILLS partnership sees this theme as an opportunity to reflect on its own 'performance' as a multi-disciplinary and inter-national research colloquium (that was supported by an equally multi-disciplinary and international advisory board). Multidisciplinary cooperation is needed to find solutions for complex problems such as that of PiE and the noPILLS partnership would like to offer their reflections on their own working (Box 8.1) as a contribution to Theme 9.

Identifying the dimensions of different perceptions of professionals in multidisciplinary projects: the noPILLS case

Introduction

noPILLS is just one example of a multidisciplinary project, and these forms of cooperation and investigation are increasingly seen as essential to deal with complex problems and design innovative solutions. However, multidisciplinary forms of cooperation, by definition, need to deal with an innate problem: professionals from different backgrounds need to communicate and understand each other. This forces them to step out of their comfort zone, find strategies to understand others and be understood by others, and to trust that the other professionals are sufficiently knowledgeable to do their job, without being able to control the work of the other.

Inviting professionals to be explicit about their arguments or their positions

In this context we took the opportunity to explore the degree to which noPILLS team members (project researchers and members of the advisory board) made judgement calls on three prime aspects in the project. This was done by provoking discussion about a number of the central elements of the 'medicinal chain' notably: actors, processes and (potential policy) intervention points.

During the exercise the participants were encouraged to assess, explore and interrogate their own (direct) experiences and their perceptions of some of these central elements of the medicinal chain; these were particularly the team members' views and experiences (perceptions) of the:

- 'risk/safety' of a range of pharmaceutical products,
- 'helpfulness' of other actors (and stakeholders), and
- 'efficiency' of processes that precede the influx of medicinal products in the sewer and subsequent aquatic environment.

In each case 10 examples were taken. Pharmaceutical products considered for 'risk/safety' included a type of antibiotic, a type of birth control, diagnostic image fluid, a pain killer, and a blood sugar medication. For actors the list included politicians, doctors, patients, pharma industry and water boards. Process examples selected from the medicinal chain included: market access/registration, human use, veterinary use, disposal, and purification of drinking water (as a [controversial] example from the extreme periphery of the medicinal chain).

Participants were asked to carry out three separate exercises to rate these three 'themes' along a continuum (i.e. ranging from "very" to "not at all") against the aforementioned perceptions of:

- the 'risk/safety' of the selected compounds,
- the 'helpfulness' of actors, and
- the 'efficiency' of the processes related to environmental influx of medicinal residue in the surface water.

In the first instance they were invited to do this based upon direct experience (and ONLY if they had this experience) and subsequently to undertake the same exercise based upon their perceptions (irrespective of actual experience).

The aim was to identify the arguments that the participants used to explain their estimation of the three factors (pharmaceutical products, actors, processes). The 'outcome of interest' was the arguments that the participants formulated, not their actual score on the respective scales. Note: for this reason, it is not useful, nor was it the aim of the exercise, to examine the scores or rankings resulting.

The visual expression of these experiences and perceptions demonstrated the wide variations in views and the central element was then to discuss the "why" of their choices. The ensuing discussion sought to draw out the (implicit) assumptions (or dimensions) participants had for making their judgements and to contrast the experience participants had with that of perceptions: particularly of those who had no direct experience.

Box 8.1

General description of results

What emerges from the exploration of the differences in experiences vis a vis perception is that, perhaps predictably, perception is often not matched by the experience. For example there was a tendency for those who had experience with particular actors as stakeholders to indicate a greater level of 'helpfulness' than those who could only offer a perceived view, indicating that perceived difficulties to 'helpfully' engage certain stakeholders were greater than actual experience of such difficulties.

Similarly in considering risk/safety of different compounds, the discussion revealed not the safety (or otherwise) of specific compounds but the differing factors that 'knowledgeable' individuals bring in to their own determinations of the key factors. There was variation in the room as to how people formulated their own notions of 'risk', placing the centrality of considerations variously upon: estimation of toxicity; the quantities in which the compound is used or the concentration in which it is found in the environment. There were similar differences of emphasis with respect to notions of 'efficiency'; terms used in the discussion were "impact", "costs", "efficient vs maximum efficiency" and "potential efficiency/impact vs actual efficiency/impact".

The discussion which resulted about the use and conceptions of the different terms, created awareness amongst the participants that colleagues may attach different meaning to these. The extent of these differences of course varied and may be the basis for minor differences in perception and possibly subsequent major differences in opinion.

Conclusions

There is clear evidence that engaging around scientifically-complex phenomena requires clear thought about what is being examined particularly in a multi-disciplinary investigation. A common understanding of central conceptual elements, or at least an acceptance of the varied interpretations of key concepts, is a crucial first step to meaningful discussion and project progress. It emerges from these exercises as equally important, the need, both in the early stages and near-end, for a mapping and remapping of the terrain. This is paramount in terms of the scientific content and also in terms of the engagement processes as central parts of any project.

For example the understanding of 'certainty', also suggests that some key conceptual elements in any future project should be explored at a very early stage to try to reach a consensus not necessarily around 'definitions' but at least to establish a recognition amongst project team members that there is considerable variation in the interpretation of such central ideas. Project members may not need to agree the meaning of 'risk' or 'danger' but they might be able to work on the basis that there are wide-ranging variations in their interpretations.

A striking finding was that in our multidisciplinary group of people, even after participating together for several years in a project with an overarching aim to come to multidisciplinary cooperation, the rating exercise created a highly heterogeneous picture and differing intellectual positions. We found in this case that different people with different backgrounds use different arguments in their judgement calls and come to different conclusions, and often these are influenced by the paradigmatic expectations of their (academic) discipline. An exercise such as that designed here specifically for noPILLS, in which implicit assumptions are made visible and therefore explicit, may be a beneficial way to start all multidisciplinary projects, to increase their 'efficiency', ensure common directional progress and agreed outputs, and optimising project outcomes.

Summary

The exercise encouraged the members of this inter- and multi-disciplinary team to consider the full breadth and 'domains' of the project and facilitated wider discussion of the project's terrain. The exercise created awareness among the majority of the project members of the existing differences in interpretations of words and concepts.

Policy pointer

- It is recommended to undertake a thorough similar exercise at the outset of inter- or multidisciplinary projects to ensure all stakeholders, for example, are engaged as the project progresses and that such reflections continue throughout the project.

Box 8.1 continued

9 noPILLS final conference – impressions and feedback

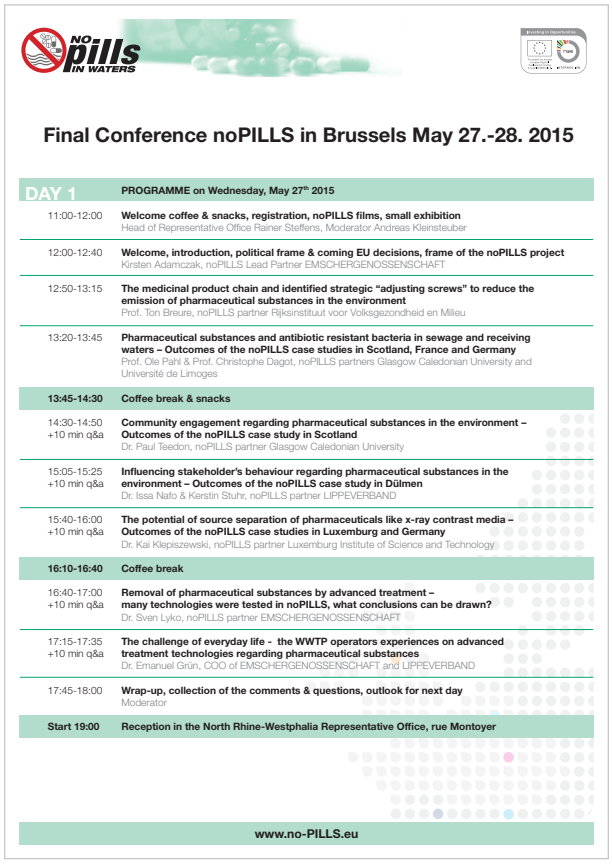
On May 27th / 28th 2015 the noPILLS final conference was held in Brussels, in the German North Rhine-Westphalian Representative Office.

On the first day the noPILLS partners presented their project outcomes, joint findings and identified gaps and challenges that have been addressed in the final report. Important messages following from these presentations and feedback from the audience were:

- Traces of pharmaceuticals are found in ecosystems and drinking water sources.
- Possible ecological effects are acknowledged.
- The spread of antibiotic-resistant germs is a current concern and will eventually become a huge problem in terms of public health.
- Special substances demand special solutions: targeted measures can be identified for specific groups of compounds.
- Costs: how much and who takes responsibility/pays?
- Which legal demands will be established and where? At the moment solutions applied are voluntary.
- Stakeholder awareness and public awareness are both important, and can be influenced.
- No silver bullet identified, but actions are identified for all stakeholders in the entire medicinal product chain.

The second day was dedicated to the political follow-up: Which conclusions can be drawn from the insights obtained, and what is the government in the involved partner countries planning to do to avoid pharmaceutical residues in the water?

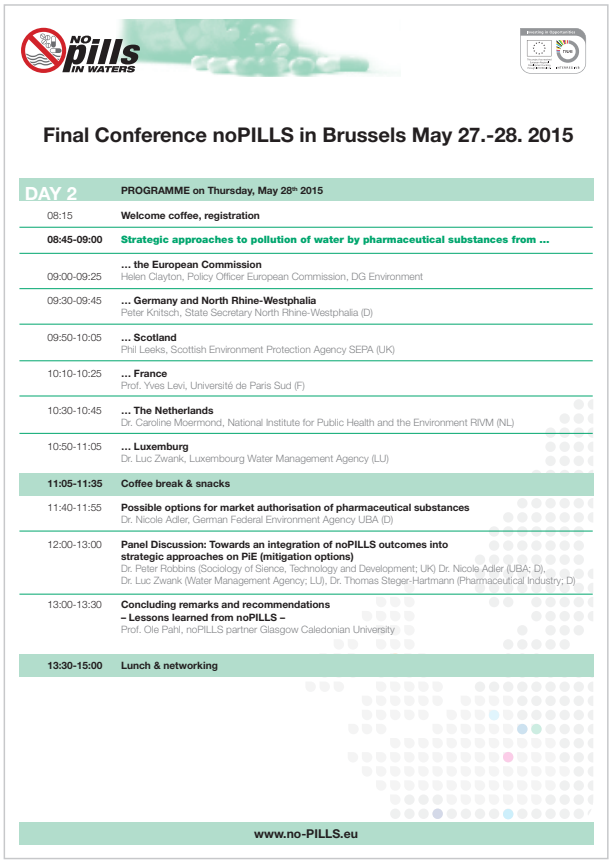
Moreover, the need to take action was seen in the bigger picture; the elimination from water should not lead to more pharmaceuticals in (sewage) sludge, landfill sites or agricultural land with the risk of transferring problems from one environmental compartment to another. In general, the aim is "less pharmaceuticals in the environment" and how to achieve this goal in the EU member states.



Final Conference noPILLS in Brussels May 27.-28. 2015

DAY 1	PROGRAMME on Wednesday, May 27th 2015
11:00-12:00	**Welcome coffee & snacks, registration, noPILLS films, small exhibition** Head of Representative Office Rainer Steffens, Moderator Andreas Kleinsteuber
12:00-12:40	**Welcome, introduction, political frame & coming EU decisions, frame of the noPILLS project** Kirsten Adamczak, noPILLS Lead Partner EMSCHERGENOSSENSCHAFT
12:50-13:15	**The medicinal product chain and identified strategic "adjusting screws" to reduce the emission of pharmaceutical substances in the environment** Prof. Ton Breure, noPILLS partner Rijksinstituut voor Volksgezondheid en Milieu
13:20-13:45	**Pharmaceutical substances and antibiotic resistant bacteria in sewage and receiving waters – Outcomes of the noPILLS case studies in Scotland, France and Germany** Prof. Ole Pahl & Prof. Christophe Dagot, noPILLS partners Glasgow Caledonian University and Université de Limoges
13:45-14:30	**Coffee break & snacks**
14:30-14:50 +10 min q&a	**Community engagement regarding pharmaceutical substances in the environment – Outcomes of the noPILLS case study in Scotland** Dr. Paul Teedon, noPILLS partner Glasgow Caledonian University
15:05-15:25 +10 min q&a	**Influencing stakeholder's behaviour regarding pharmaceutical substances in the environment – Outcomes of the noPILLS case study in Dülmen** Dr. Issa Nafo & Kerstin Stuhr, noPILLS partner LIPPEVERBAND
15:40-16:00 +10 min q&a	**The potential of source separation of pharmaceuticals like x-ray contrast media – Outcomes of the noPILLS case studies in Luxemburg and Germany** Dr. Kai Klepiszewski, noPILLS partner Luxemburg Institute of Science and Technology
16:10-16:40	**Coffee break**
16:40-17:00 +10 min q&a	**Removal of pharmaceutical substances by advanced treatment – many technologies were tested in noPILLS, what conclusions can be drawn?** Dr. Sven Lyko, noPILLS partner EMSCHERGENOSSENSCHAFT
17:15-17:35 +10 min q&a	**The challenge of everyday life - the WWTP operators experiences on advanced treatment technologies regarding pharmaceutical substances** Dr. Emanuel Grün, COO of EMSCHERGENOSSENSCHAFT and LIPPEVERBAND
17:45-18:00	**Wrap-up, collection of the comments & questions, outlook for next day** Moderator
Start 19:00	**Reception in the North Rhine-Westphalia Representative Office, rue Montoyer**

www.no-PILLS.eu

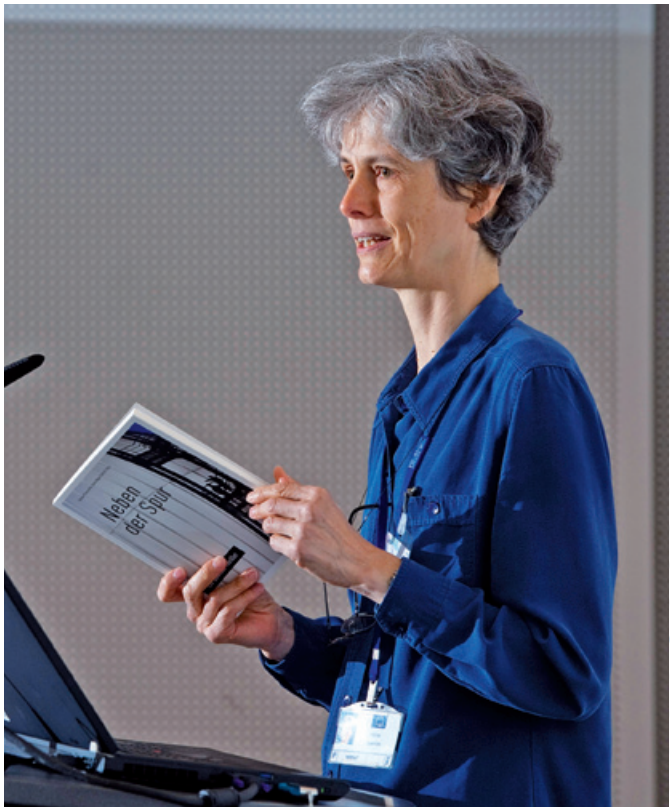


Final Conference noPILLS in Brussels May 27.-28. 2015

DAY 2	PROGRAMME on Thursday, May 28th 2015
08:15	**Welcome coffee, registration**
08:45-09:00	**Strategic approaches to pollution of water by pharmaceutical substances from ...**
09:00-09:25	**... the European Commission** Helen Clayton, Policy Officer European Commission, DG Environment
09:30-09:45	**... Germany and North Rhine-Westphalia** Peter Knitsch, State Secretary North Rhine-Westphalia (D)
09:50-10:05	**... Scotland** Phil Leeks, Scottish Environment Protection Agency SEPA (UK)
10:10-10:25	**... France** Prof. Yves Levi, Université de Paris Sud (F)
10:30-10:45	**... The Netherlands** Dr. Caroline Moermond, National Institute for Public Health and the Environment RIVM (NL)
10:50-11:05	**... Luxemburg** Dr. Luc Zwank, Luxembourg Water Management Agency (LU)
11:05-11:35	**Coffee break & snacks**
11:40-11:55	**Possible options for market authorisation of pharmaceutical substances** Dr. Nicole Adler, German Federal Environment Agency UBA (D)
12:00-13:00	**Panel Discussion: Towards an integration of noPILLS outcomes into strategic approaches on PiE (mitigation options)** Dr. Peter Robbins (Sociology of Sience, Technology and Development; UK) Dr. Nicole Adler (UBA: D), Dr. Luc Zwank (Water Management Agency; LU), Dr. Thomas Steger-Hartmann (Pharmaceutical Industry; D)
13:00-13:30	**Concluding remarks and recommendations – Lessons learned from noPILLS –** Prof. Ole Pahl, noPILLS partner Glasgow Caledonian University
13:30-15:00	**Lunch & networking**

www.no-PILLS.eu

Helen Clayton, Policy Officer, European Commission, DG Environment, summarised the EU's progress to date on developing a strategic approach to the pollution of water by pharmaceutical substances as required by Directive 2013/39/EU. Although there would be a few months' delay, plans had been made to gather additional information to support the work. Helen Clayton stressed the value to the Commission of inputs from research projects such as noPILLS, and welcomed the commitment of the scientists and practitioners involved to continue working on the issue in their regions. The challenge is always to translate research findings into policy. The approaches discussed in the noPILLS project already show that a wide range of tools across various sectors and timescales is needed, and that raising awareness among all relevant stakeholders including producers, healthcare professionals and patients will be particularly important.



The noPILLS project has demonstrated the effectiveness of awareness raising in influencing behaviour; experience in other areas such as recycling confirms that children can be particularly effective at communicating messages to their parents. It's important that we all "speak the same language", for example by using commonly understood words or simple logos in product leaflets. We shouldn't forget about the influence of lifestyle on people's health, and the possibility of reducing the need for treatment – and thus emissions to water - by living more healthily."

Peter Knitsch, State Secretary in the Environment Ministry in North Rhine-Westphalia (NRW)/Germany, pointed out the special feature this Federal State has. Here pharmaceuticals are in general seen in the wider frame of micro pollutants that also for example from household chemicals, brownfields, agriculture or industry. In NRW the cooperation within the International Commission for the Protection of the Rhine (ICPR) plays a leading role on strategic approaches and hereby for the transnational policy, too. The NRW environment policy is – besides education and legal measures regarding certain substances – very much focusing on treatment technologies at the source and in municipal treatment facilities.

"For precautionary reasons we need to start with multi-barrier-principles today already. We are aware that this causes far higher costs. But on the other hand: Which corporate costs will it cause if we don't take action?"

Phil Leeks from the Scottish Environment Protection Agency SEPA explained the Scottish network that supports the work on pharmaceutical residues, with the primary aim to identify the problem, available data and possible hot spots in order to develop abatement strategies where applicable.

"Detailed sewer catchment investigations enable us to better understand where pharmaceutical substances arise. We need to identify the most appropriate solutions to prevent pharmaceuticals entering the water environment, these should be source orientated rather than end-of-pipe treatment."

Prof. Yves Levi, Université de Paris Sud, outlined key aspects of the public perception of pharmaceuticals in the environment within France. National initiatives, jointly governed by the Ministry of Health and the Ministry of Environment still leave several gaps to close in addressing the 2011. Both jointly elaborate strategies but to set up the 2011 decided national action plan (to reduce pharmaceuticals in water) there are. Moreover, addressing the wider public in order to achieve awareness and behaviour changes is difficult as the press often simplifies the background stories.

"In these growing markets of pharmaceuticals and many other chemical compounds that enter the water we have to communicate very precisely what receiving environment we talk about, who bears responsibility and which threshold values to meet where. In public the most attention is paid whenever tap water is mentioned."

Dr. Caroline Moermond, National Institute for Public Health and the Environment RIVM (NL), stressed that the Netherlands are in a special situation as they are the "receiving environment" regarding water coming from the Rhine and Meuse catchments.

"We already work in the spirit of the noPILLS approach. The Netherlands try to solve problems with a "round table approach" that involves all actors. Moreover, we have examples where an integrated way of thinking has shown that what is good for the environment can also have positive side effects for public health. That's also a way to manage the cost-benefit discussion."

Dr. Luc Zwank, Luxembourg Water Management Agency (LU), is also representative in working groups of the International commission for the Protection of the Rhine and therefore he is very familiar with transnational strategies.

"Our Luxemburgish strategy is going into a "no regret" direction at the moment, for example reserving space on the new sites of waste water treatment plants in order to have space when we once come to decisions about advanced treatment needs. We are hoping for an EU frame within the Water Framework Directive to guide the elimination demands."

Possible options for market authorisation of pharmaceutical substances

Dr. Nicole Adler, German Federal Environment Agency UBA (D), summarized the current legal situation and the need to take action regarding the legislative frame.

„We have identified a number of regulatory gaps. For example by now, even if a new substance is known to be environmentally problematic, no refusal of the product is possible. A comprehensive environmental assessment is available for 200 pharmaceutical ingredients. For some hundred out of those pharmaceuticals with market authorization permitted before 2006 there has no environmental assessment been performed. To close this gap we urgently need better data and legislative changes."

Panel Discussion: Towards an integration of noPILLS outcomes into strategic approaches on Pharmaceuticals in the Environment

Key messages of the panel discussion

Dr. Peter Robbins, Sociology of Sience, Technology and Development (UK)

"Public science and technology engagement campaigns have sometimes been overtaken by interest groups, which has meant that issues have become polarised. Our research on the UK GM crops debate found that public attitudes on science-based issues was shaped more by the source of the information than the content. As such, we found that public trust in sources of information is important and is built over time. So the message is important, but also its source."

Dr. Nicole Adler, UBA (D)

"Even if we don't see any threat by now – long term we have to estimate there will be problems we simply cannot imagine now. The cocktail is difficult to assess and to communicate."

"For bottled water there are threshold values that don't exist for tab water."

Dr. Luc Zwank, Water Management Agency (LU),

"We are all benefitting from newly developed substances but all of them will end up somehow in the environment. So it is again looking at the whole life cycle and the cost-benefit ratio. But in the end we are not prepared to work constantly, we always have to react to shots coming from somewhere"

Dr. Thomas Steger-Hartmann, Bayer HealthCare (D), representing the Pharmaceutical Industry:

"Concerning drinking water, we can exclude a risk for human health in Europe, however, there may be an impact on aquatic species in surface waters receiving large volumes of effluent from sewage treatment plants."

"We do have many substances on the market for decades now, they are well monitored and the traces we find are not problematic for humans, even if bioaccumulation might occur in some aquatic species."

“Which actions to take - my priorities”

Dr. Thomas Steger-Hartmann

“We need to close the data gaps for substances permitted before 2006.”

“We also need to assess the release from pharmaceutical manufacturing sites, particularly in less developed countries, where sewage treatment does not necessarily meet European standards.”

“If we manage to have end-of-pipe solutions for a costs increase of up to 10% it is a good contribution to the reduction of many residues in the aquatic environment.”

Dr. Luc Zwank

“In general I agree to the mentioned priorities. The challenge is to have the right measure at the right place and a consideration of interdependencies.”

Dr. Nicole Adler

“There is a need to address every step of the life cycle and think both short and long term.”

Dr. Peter Robbins

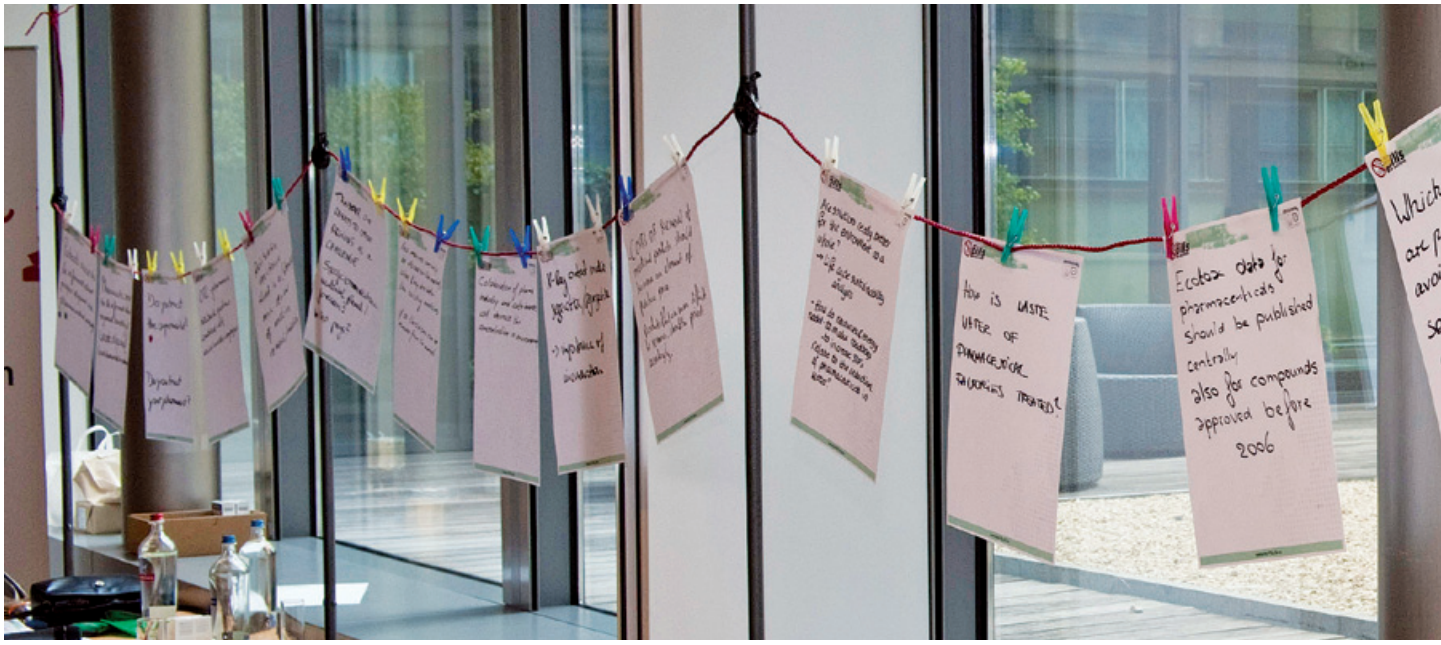
“It is important to involve economists as a next step in this work. They can carry out cost-benefit analysis and willingness to pay surveys. It is important to think about how best to engage publics. It is not always about simply providing scientific information; how the information is provided, by whom and at what stage are all important considerations.”

Remark:

The final report was printed as a conference version for the May 27th / 28th 2015 symposium and it was announced at the conference that additional inputs and photos would be collected and added to the version that is now disseminated via the webpage www.no-PILLS.eu.

This final report is only summarizing a part of the project work; scientific publications will follow hereafter. We are grateful for further support and all participating partners are happy to answer questions and impart knowledge.

Feedback from the audience – comments and questions



Patients need to be informed about proper disposal via pharmaceutical industry	Pharmacists need to be informed about regional handling of waste disposal (and disseminate to customers)	When I'm drinking water I have no choice in case there are substances in it. Informing public is about enabling them to choose.	Are solutions really better for the environment as a whole? -> Life cycle sustainability analysis
Can we group compounds and look into the product chain: where and how is elimination useful?	How do resources and energy needed (to make roadbags or to increase waste water treatment plants) relate to the reduction of pharmaceuticals in water?	If we go for the "single compounds approach" we are always behind.	Costs of removal of medicinal products should become an element of purchase price. Products that are more difficult to remove should be priced accordingly.
How is waste water of pharmaceutical factories treated?	Public knowledge about water is poor in general, so public debates should be well organized to avoid developments like about climate change where trust in stakeholders gets lost and everyone points to another.		There are promising approaches – a public-private-partnership between the pharmaceutical industry, the European Commission and regulatory administrations

Which strategies are planned to avoid problems from sewage sludge?	X-ray contrast media separation/segregation -> importance of incineration	Ecotox data for pharmaceuticals should be published centrally also for compounds approved before 2006	New medicines can only be allowed on the market, when they are better than existing medicines. If so the old ones can be removed from the market.
Antibiotic resistance threat is a (should) main driver of medicines removal / reduction.	Transfer of results to other regions as a challenge. Specific communication material planned/ foreseen? Who pays?	Do you trust the supermarket? Do you trust your pharmacist?	OTC and pharmacies take back systems combined with social media campaigns
Which role play pharmacists in advice, in the sales talk in comparison to super markets, for disposal habits?	Collaboration of pharma industry and water boards will decrease the concentration in environment	Which strategies are planned or needed to avoid a transfer from one environmental medium to another, for example eliminating substances from waste water but finding them later in sewage sludge or on waste disposal sites?	

References

References Chapter 1

BIO Intelligence Service (2013), Study on the environmental risks of medicinal products, Final Report prepared for Executive Agency for Health and Consumers

PILLS, (2012), Pharmaceutical Input and Elimination from Local Sources. Final report of the cooperation project PILLS. Emschergenossenschaft, Essen, Germany.

References Chapter 2

Berezowska A. 2009. Voorkomen beter dan genezen. Het Health Belief Model en de omgang met medicijnrestanten (Masterthesis) [Online]. Enschede: Universiteit Twente. Available: http://essay.utwente.nl/59535/1/MA_scriptie_A_Berezowska.pdf.

BIO Intelligence Service (2013), Study on the environmental risks of medicinal products, Final Report prepared for Executive Agency for Health and Consumers

Butler, C. C., Rollnick, S., Pill, R., Maggs-Rapport, F. & Stott, N. 1998. Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. BMJ, 317, 637-42.

Buurma H., de Gier J.J. & Egberts A.C.G. 2005. De apotheek als zorgpraktijk. In: Buurma H., Beudeker H.J., De Jong-van den Berg L.T.W. & Leufkens H.G.M. (eds.) Het Geneesmiddel. 4 ed. Maarssen: Elsevier Gezondheidszorg.

Denig P. & Haaijer-Ruskamp F.M. 2005. Voorschrijven van geneesmiddelen. In: Buurma H., Beudeker H.J., De Jong-van den Berg L.T.W. & Leufkens H.G.M. (eds.) Het Geneesmiddel. 4 ed. Maarssen: Elsevier Gezondheidszorg.

DGV, 2006. Verspilling van geneesmiddelen: de stand van zaken in 2004. DGV, Nederlands instituut voor verantwoord medicijngebruik. Utrecht. http://www.stevenshof.nl/rapport.teruggebrachte%20gnm.2006.pdf

Dickinson, H. O., Mason, J. M., Nicolson, D. J., Campbell, F., Beyer, F. R., Cook, J. V., Williams, B. & Ford, G. A. 2006. Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. J Hypertens, 24, 215-33.

Expatica, 2012. The Healthcare system in Luxembourg. www.expatica.com/lu/visas-and-permits/Healthcare-in-Luxembourg_105466.html.

Gillies, C. L., Abrams, K. R., Lambert, P. C., Cooper, N. J., Sutton, A. J., Hsu, R. T. & Khunti, K. 2007. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ, 334, 299.

KNMG, 2015: http://knmg.artsennet.nl/Diensten/KNMG-Artseninfolijn-10/Casus-Artseninfolijn/37760/Wie-mogen-geneesmiddelen-voorschrijven.htm. Consulted 12-5-2015

Lado, E., Vacariza, M., Fernandez-Gonzalez, C., Gestal-Otero, J. J. & Figueiras, A. 2008. Influence exerted on drug prescribing by patients' attitudes and expectations and by doctors' perception of such expectations: a cohort and nested case-control study. J Eval Clin Pract, 14, 453-9.

Lambooij A., Essink R., Nijpels M. & de Metz J. 2014. Monitor Voorschrijfgedrag Huisartsen 2014. Utrecht: Instituut voor Verantwoord Medicijngebruik.

Little, P., Dorward, M., Warner, G., Stephens, K., Senior, J. & Moore, M. 2004. Importance of patient pressure and perceived pressure and perceived medical need for investigations, referral, and prescribing in primary care: nested observational study. BMJ, 328, 444.

Mannu, G. S., Zaman, M. J., Gupta, A., Rehman, H. U. & Myint, P. K. 2013. Evidence of lifestyle modification in the management of hypercholesterolemia. Curr Cardiol Rev, 9, 2-14.

Mul, S. 2014. Wel gerekend, niet gegeven [Online]. De Consumentenbond. Available: http://www.consumentenbond.nl/morello-bestanden/gidsarchief/gezondgids/2014/ng201408p30_Test_eerste_uitgifte_medicijnen.pdf;jsessionid=D958E8551C97662564B83F6D60B7531B?bodyClass=dossiers+overview [Accessed September 2014].

NCPF. 2014. Voorlichting aan patiënt bij medicijnuitgifte nog niet in orde. [Online]. Available: http://www.npcf.nl/index.php?option=com_aiportfolio&view=article&Itemid=2&id=81:Medicijnen&standpunt=5678 [Accessed 15 September 2014].

NCPIE (National Council on Patient Information and Education). 2002. Attitudes and Beliefs About the Use of Over-the-Counter Medicines: A Dose of Reality. A National Survey of Consumers and Health Professionals [Online]. Harris Intercative Market Research. Available: http://www.bemedwise.org/survey/final_survey.pdf [Accessed September 2014.

NZA, 2014. Marktscan en beleidsbrief extramurale farmaceutische zorg. Weergave van de markt 2010-2014. (http://www.nza.nl/104107/105773/953131/Marktscan_en_beleidsbrief_Farmacie.pdf)

OECD (2014), "OECD Health Data: Health care utilisation", OECD Health Statistics (database). DOI: http://dx.doi.org/10.1787/data-00542-en. (Accessed on 13 May 2015)

Ornish, D., Brown, S. E., Scherwitz, L. W., Billings, J. H., Armstrong, W. T., Ports, T. A., McLanahan, S. M., Kirkeeide, R. L., Brand, R. J. & Gould, K. L. 1990. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. Lancet, 336, 129-33.

Paes A.H.P. & Smit C. 2005. De patiënt, zijn ziekte en geneesmiddelengebruik. In: Buurma H., Beudeker H.J., De Jong-van den Berg L.T.W. & Leufkens H.G.M (eds.) Het Geneesmiddel. 4 ed. Maarssen: Elsevier Gezondheidszorg.

PCO Certifying Body 2015. Waarborgeisen gecertificeerde drogisterijen inzake het ter hand stellen van niet-receptgeneesmiddelen en publieksreclame voor niet-receptgeneesmiddelen en gezondheidsproducten. Maarssen: Centraal Bureau Drogisterijbedrijven.

PILLS, (2012), Pharmaceutical Input and Elimination from Local Sources. Final report of the cooperation project PILLS. Emschergenossenschaft, Essen, Germany.

Reitsma M., Brabers A., Korevaar J., de Jong J., van Dijk M. & van Dijk L. 2013. Een derde van de geneesmiddelengebruikers houdt geneesmiddelen over. Utrecht: NIVEL.

RIVM in prep. Medicinal product chain. Report RIVM in preparation

Sanofi. 2014. Geneesmiddelendebat. Prijs en vergoedingsbeleid. [Online]. Available:http://www.geneesmiddelendebat.nl/toegang-tot-geneesmiddelen/ziekenhuisgeneesmiddelen [Accessed 15 September 2014].

Schafer, W., Kroneman, M., Boerma, W., van den Berg, M., Westert, G., Deville, W. & van Ginneken, E. 2010. The Netherlands: health system review. Health Syst Transit, 12, v-xxvii, 1-228.

The Human Medicines Regulations 2012: www.legislation.gov.uk/uksi/2012/1916/contents/made.

Tong, A. Y., Peake, B. M. & Braund, R. 2011. Disposal practices for unused medications around the world. Environ Int, 37, 292-8.

Trivedi, H., Trivedi, A. & Hannan, M. F. 2014. Readability and comprehensibility of over-the-counter medication labels. Ren Fail, 36, 473-7.

Van den Berg M.J., de Boer D., Gijsen R., Heijink R., Limburg L.C.M. & Zwakhals S. 2014. Zorgbalans 2014. De prestaties van de Nederlandse gezondheidszorg. Bilthoven: RIVM.

Vogler S, Schmickl B. (2010) Rational use of medicines in Europe. Gesundheit Österreich GmbH/Österreichisches Bundesinstitut für Gesundheitswesen (GÖG/ÖBIG).

Vogler S., Leopold C., Zuidberg C. & Habl C. 2014. Medicines discarded in household garbage: analysis of a pharmaceutical waste sample in Vienna. Journal of Pharmaceutical Policy and Practice 7.

Webb, S. & Lloyd, M. 1994. Prescribing and referral in general practice: a study of patients' expectations and doctors' actions. Br J Gen Pract, 44, 165-9.

WHO, 2010. Schäfer W, Kroneman M, Boerma W, van den Berg M, Westert G, Devillé Wand van Ginneken E. The Netherlands: Health system review. Health Systems in Transition, 2010; 12(1):1–229. (http://www.euro.who.int/__data/assets/pdf_file/0008/85391/E93667.pdf)

YHEC/School of Pharmacy, University of London (2010). Evaluation of the Scale, Causes and Costs of Waste Medicines. University of York and The School of Pharmacy, University of London, London. http://discovery.ucl.ac.uk/1350234/1/Evaluation_of_NHS_Medicines_Waste__web_publication_version.pdf

Zorginstituut, 2014. GIPeilingen 2013. Ontwikkelingen genees- en hulpmiddelengebruik. Genees- en hulpmiddelen Informatie Project | oktober 2014 | nr. 35. De Bondt, Barendrecht.

(http://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/gipeilingen/1410-gipeilingen-2013/GIPeilingen+2012.pdf)

Zorgverzekeraars Nederland. 2014. Zorgverzekeringswet: Medicijnen. [Online]. Zeist. Available: https://www.zn.nl/consumenteninfo/zorgverzekering/#section=tabs-1 [Accessed 1 September 2014].

References Chapter 3

Allen H.K., Donato J., Wang, H.H., Cloud-Hansen, K.A., Davies, J., Handelsman, J. (2010) Call of the wild: Antibiotic resistance genes in natural environment. Nat. Rev. Microbiol. 8, 251-259

ANSM - National Agency for Medicines Safety (2014) L'évolution des consommations d'antibiotiques en France entre 2000 et 2013. Report November 2014, ansm.sante.fr

Baquero, F., Martinez J.L., Canton, R. (2008) Antibiotics and antibiotic resistance in water environments. Curr Opin Biotechnol 19: 260–265.

Bellingham, M., McKinnell, C., Fowler, P.A., Amezaga, M.R., Zhang, Z., Rhind, S.M., Cotinot, C., Mandon-Pepin, B., Evans NP, Sharpe RM (2012) Foetal and post- natal exposure of sheep to sewage sludge chemicals disrupts sperm production in adulthood in a subset of animals. International journal of Andrology Vol. 35 Issue 3 Pp. 317-329

Berendonk, T.U., Manaia, C.M., Merlin, C., Fatta-Kassinos, D., Cytryn, E., Walsh, F., Bürgmann, H., Sørum, H., Norström, M., Pons, M.N., Kreuzinger, N., Huovinen, P., Stefani, S., Schwartz, T., Kisand, V., Baquero, F., Martinez, J.L. (2015) Tackling antibiotic resistance: the environmental framework. Nature Reviews, 13, 310-317

BIO Intelligence Service (2013) Study on the environmental risks of medicinal products. Final Report prepared for Executive Agency for Health and Consumers

Buckley, M. (2009) Antibiotic Resistance: An Ecological Perspective on an old Problem. American Academy of Microbiology, Washington.

Chomarat M. (2014) Colloque "Santé et Biodiversité. Lyon, France

Christensen A.M., Faaborg-Andersen , S., Ingerslev, F., Baun, A. (2007) Mixture and single-substance toxicity of selective serotonin reuptake inhibitors toward algae and crustaceans. Environmental Toxicology and Chemistry, Vol. 26, No. 1, pp. 85–91

Cleuvers M. (2004) Mixture toxicity of the anti-inflammatory drugs diclofenac, ibuprofen, naproxen, and acetylsalicylic acid. Ecotoxicology and Environmental Safety 59 (2004) pp. 309–315

DOH (2011) Antimicrobial stewardship: Start smart - then focus. UK Department of Health, London

EC (2015) Commission implementing decision (EU) 2015/495 of 20 March 2015 establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council.

Grung, M., Heimstad, E.S., Moe, M., Schlabach, M., Svenson, A., Thomas, K., Woldegiorgis, A. (2007) Human and Veterinary Pharmaceuticals, Narcotics, and Personal Care Products in the Environment. TA-2325/2007. Norwegian Pollution Control Authority, Oslo, Norway

FASS Allmänhet (2013). [Cited 17 Feb 2014]. Available from: http://www.fass.se/LIF/startpage?5

Ferrari B, Paxéus N, Giudice RL, Pollio A, Garric J. 2003. Ecotoxicological impact of pharmaceuticals found in treated wastewaters: study of carbamazepine, clofibric acid, and diclofenac. Ecotoxicol.Environ.Saf., Vol. 55 No. 3 pp. 359-370

Halling-Sørensen, B., Holten-Lützhøft, H.-C., Andersen, H. R., and Ingerslev, F. (2000) Environmental risk assessment of antibiotics: comparison of mecillinam, trimethoprim and ciprofloxacin. Journal of Antimicrobial Chemotherapy 46, Suppl. S1, 53-58.

Isidori, M., Nardelli A., Pascarella, L., Rubiono, M., and Parrella, A. (2007) Toxic and genotoxic impact of fibrates and their photoproducts on non-target organisms. Environmental International 33: 635-641

Lachassagne D. (2014) Devenir de micropolluants presents dans les boues d'épuration, du traitement à l'épandage agricole (…). Thesis of l'Université de Limoges

Novo, A., Manaia, C. (2010) Factors influencing antibiotic resistance burden in municipal wastewater treatment plants. Appl Microbiol Biotechnol 87: 1157–1166.

PILLS, (2012), Pharmaceutical Input and Elimination from Local Sources. Final report of the cooperation project PILLS. Emschergenossenschaft, Essen, Germany.

Schwartz, T., Kohnen, W., Jansen, B., Obst, U (2003) 3Detection of antibiotic-resistant bacteria and their resistance genes in wastewater, surface water and deinking water biofilms. FEMS Microbiol. Ecol. 43, 325-335.

Stalder, T., Barraud, O., Jove, T., Casellas, M., Gaschet, M., Dagot, C., Ploy, M.C. (2013) Quantitative and qualitative impact of hospital effluent on dissemination of the integron pool. The ISME Journal 1–10

Stokes, H.W., Gillings, M. (2011) Gene flow, mobile genetic elements and the recruitment of antibiotic resistance genes into Gram- negative pathogens. FEMS Microbiol Rev 35:790–819.

Ternes, T.A., Herrmann, N., Bonerz, M., Knacker, T., Siegrist, H., Joss, A.(2004) A rapid method to measure the solid-water distribution coefficient (Kd) for pharmaceuticals and musk fragrances in sewage sludge. Water Research, Vol. 38, 2004, pp. 4075–4084.

TWH (2014) National Strategy for Combating Antibiotic Resistant Bacteria. The White House, Washington, USA.

Verlicchi, P., Al Aukidy, M., Zambello, E. (2012) Occurrence of pharmaceutical compounds in urban wastewater: removal, mass load and environmental risk after a secondary treatment – a review. Science of the Total Environment 429, pp. 123-155

Wright, G.D. (2007). The antibiotic resistome: the nexus of chemical and genetic diversity. Nat. Rev. Microbiol. 5, 175-186

WHO (2015) Drug Resistance. [online] Available from http://www.who.int/drugresistance/infosharing/en/. [Accessed 13/05/2015].

References Chapter 4

Burglé M., Brugnaux S. (2013) "Baromètre de notoriété et des comportements à l'égard de Cyclamed", LH2, 13 février 2009 www.cyclamed.org/barometre-lh2-2256.

ISOE (2014.): Medikamenten-Entsorgung – Verbraucherwissen mangelhaft. Institut für sozial-ökologische Forschung GmbH. Pressemitteilung 27. Mai 2014. Frankfurt a.M., http://www.isoe.de/presse/news/news-single/medikamenten-entsorgung-verbraucherwissen-mangelhaft.

Vega, A. (2012). Positivisme et dépendance: les usages socioculturels du médicament chez les médecins généralistes français Sciences sociales et santé, 30, 71-102.

References Chapter 5

BIO Intelligence Service (2013). Study on the environmental risks of medicinal products. Final Report prepared for Executive Agency for Health and Costumers.
PILLS (2012). Pharmaceutical Input and Elimination from local sources. Finalreport of the European cooperation project PILLS, Emschergenossenschaft, Essen, Germany.

Helwig K., Hunter C., MacLachlan J., McNaughtan M., Roberts J., Cornelisson A., Dagot C., Evenblij H., Klepiszewski K., Lyko S., McArdell C., Nafo I., Venditti S. and Pahl O. (2013). Micropollutants of urban origin: identification of priority substances in the healthsector. Journal of Environmental & Analytical Toxicology, Volume 3, Issue 4.

IKSR (2010). Auswertungsbericht Röntgenkontrastmittel. Bericht Nr. 187. Internationale Kommission zum Schutz des Rheins (IKSR). Koblenz. Germany.
Joss A., Zabczynski S., Göbel A., Hoffmann B., Löffler D., McArdell C., Ternes T. A., Thomsen A. and Siegrist, H. (2006). Biological degradation of pharmaceuticals in municipal wastewater treatment: Proposing a classification scheme. Water Research, 40, pp. 1686-1696.

Köhler C., Venditti S., Igos E., Klepiszewski K., Benetto E. and Cornelissen A. (2012). Elimination of Pharmaceutical Residues in Hospital Wastewater using advanced UV Irradiation Technology. Journal of Hazardous Materials, Volume 239 – 240, pp. 70-77

Kovalova, L., Siegrist, H., Singer, H., Wittmer, A., & McArdell, C. S. (2012). Hospital wastewater treatment by membrane bioreactor: performance and efficiency for organic micropollutant elimination. Environmental Science & Technology, 46(3), 1536–45. doi:10.1021/es203495d

Lienert J., Bürki T. and Escher B.I. (2007). Reducing micropollutants with source control: substance flow analysis of 212 pharmceuticals in faeces and urine. Water Science & Technology, Vol. 55, No. 5, pp. 87-96.

Schuster P., Heinzmann B., Schwarz R.-J., Wiemann M. and Schulz, C. (2006). Getrennte Erfassung von jodorganischen Rontgenkontrastmitteln in Krankenhausern - Phase 2: Praktische Durchfuhrung. Abschlussbericht, Berlin, Germany.

Weissbrodt D., Kovalova L., Ort C., Pazhepurackel V., Moser R., Hollender J., Siegrist H.and Mcardell C. (2009). Mass Flow of X-Ray Contrast media in Hospital Wastewater. Journal of Environmental Science and Technology, 43 (13), pp. 4810–4817.

References Chapter 6

Abu Hasan, H.; Sheikh Abdullah, S. R.; Kamarudin, S. K.; Kofli, T. N. (2009): A review on the design criteria of biological aerated filter for COD, ammonia and manganese removal in drinking water treatment. Journal – The institution of Engineers, Malaysia, Vol. 70, No. 4.

Alrhmoun M., Carrion C., Casellas M., Dagot C. (2015). Upgrading the performances of ultrafiltration membrane system coupled with activated sludge reactor by addition of biofilm supports for the treatment of hospital effluents. Chemical Engineering Journal 262, 456–463.

BARRAUD O., CASELLAS M., DAGOT C., PLOY M.C., An Antibiotic-Resistant Class 3 Integron in an Enterobacter cloacae Isolate from Hospital Effluent. Accepted in Clinical Microbiology and Infection, Clinical Microbiology and Infection, 19 (2). (2013) - (IF 4,54)

Carvalho, R. N., Ceriani, L., Ippolito, A., & Lettieri, T. (2014). Development of the 1 st Watch List under the Environmental Quality Standards Directive of water policy. Brussels.

Dussert, B. and Van Stone, G. (1994): The biological active carbon process for water purification. Water Engineerin & Management. 141 (12),pp 22-24

Göbel, A.; Thomsen, A.; Mcardell, C.S.; Joss, A.; Giger, W. (2005): Occurrence and Sorption Behaviour of Sulfonamides, Macrolides and Trimethoprim in Activated Sludge Treatment, Environ. Sci. Technol. 39, pp 3981-3989.

Jiang, J.-Q. (2013). The Role of Ferrate(VI) in the Remediation of Emerging Micro Pollutants. Procedia Environmental Sciences, 18, 418–426. doi:10.1016/j.proenv.2013.04.056

Kennedy, A.M.; Reinert A.M; Knappe, D.R.U.; Ferrer, I.; Scott Summers, R. (2015): Full and pilot scale GAC adsorption of organic micropollutants. Water Research, Volume 68, pp. 238–248.

Köhler, C.; Venditti, S.; Igos E, Klepiszewski, K.; Benetto, E.; Cornelissen, A. (2012): Elimination of pharmaceutical residues in hospital wastewater using advanced UV irradiation technology: a comparative assessment. Journal of hazardous Materials, 239-240, pp 70-77

Kovalova, L., Siegrist, H., Singer, H., Wittmer, A., & McArdell, C. S. (2012). Hospital wastewater treatment by membrane bioreactor: performance and efficiency for organic micropollutant elimination. Environmental Science & Technology, 46(3), 1536–45. doi:10.1021/es203495d

Li, C., Cabassud, C., & Guigui, C. (2014). Evaluation of membrane bioreactor on removal of pharmaceutical micropollutants : a review. Desalination and Water Treatment, 1–14. doi:10.1080/19443994.2014.926839

Magdeburg, A., Stalter, D., Schlüsener, M., Ternes, T., & Oehlmann, J. (2013). Evaluating the efficiency of advanced wastewater treatment: Target analysis of organic contaminants and (geno-)toxicity assessment tell a different story. Water Research, In Press. doi:10.1016/j.watres.2013.11.041

Margot, J., Kienle, C., Magnet, A., Weil, M., Rossi, L., Felippe, L., … Barry, D. A. (2013). Treatment of micropollutants in municipal wastewater : Ozone or powdered activated carbon? Science of The Total Environment, 462, 480–498.

Nafo, I., & Lyko, S. (2012). Full-scale plant for the elimination of pharmaceuticals in hospital wastewater – Comparison of advanced treatment technologies. In 16th International Symposium on Sustainable Water Management – New Solutions for new problems.

Nafo, I., Lyko, S., Evenblij, H., Cornelissen, A., Igos, E., Klepiszewski, K., Ploy, M.-C. (2012). Pharmaceutical Input and Elimination from local sources. Essen.

Rattier, M., Reungoat, J., & Gernjak, W. (2012). Organic Micropollutant Removal by Biological Activated Carbon Filtration : A Review Urban Water Security Research Alliance Technical Report No . 53. Queensland.

Reungoat, J., Escher, B. I., Macova, M., & Keller, J. (2011). Biofiltration of wastewater treatment plant effluent: effective removal of pharmaceuticals and personal care products and reduction of toxicity. Water Research, 45(9), 2751–62. doi:10.1016/j.watres.2011.02.013

Simpson, D. (2008): Biofilm processes in biologically active carbon water, Water Research 42, pp 2839-2848.

Stalder T., Alrhmoun M., Louvet J.N., Casellas M., Maftah C., Carrion C., Pons M.N., Pahl O., Ploy M.C.; Dagot C. Dynamic assessment of the floc morphology, bacterial diversity and integron content of an activated sludge reactor processing hospital effluent. Environmental Science & Technology, pp 7909-7917, (2013)

Stalder T., BARRAUD O., JOVE T., CASELLAS M., GASCHET M., DAGOT C., PLOY M.C. Quantitative and qualitative impact of hospital effluent on dissemination of the integron pool. The ISME Journal (2013), 1–10

Venditti, S.; Arenz-Leufen, M.; Klepiszewki, K.; Cornelissen, A. (2012): Treatment of pharmaceutical wastewater by O3 and O3/H2O2 processes: a pilot scale study in Luxembourg. Proceedings of the International Conference on Ecotechnologies for Wastewater Treatment, Santiago de Compostela, Spain.

Verlicchi, P., Al Aukidy, M., Galletti, A., Petrovic, M., & Barcelo, D. (2012). Hospital effluent: investigation of the concentrations and distribution of pharmaceuticals and environmental risk assessment. The Science of the Total Environment, 430, 109–18. doi:10.1016/j.scitotenv.2012.04.055

Verlicchi, P., Al Aukidy, M., & Zambello, E. (2012). Occurrence of pharmaceutical compounds in urban wastewater: removal, mass load and environmental risk after a secondary treatment--a review. The Science of the Total Environment, 429, 123–55. doi:10.1016/j.scitotenv.2012.04.028

Verlicchi, P., Al Aukidy, M., & Zambello, E. (2015). What have we learned from worldwide experiences on the management and treatment of hospital effluent? — An overview and a discussion on perspectives. Science of The Total Environment, 514, 467–491. doi:10.1016/j.scitotenv.2015.02.020

List of authors (corresponding authors underlined)

Chapter 1

Dagot C., EA 4330, Université de Limoges, FRANCE

van der Grinten E., RIVM, Netherlands

Helwig K.P.M., Glasgow Caledonian University, UK

Klepiszewski K., Luxembourg Institute of Science and Technology, Luxembourg

Lyko S., Emschergenossenschaft, Germany

Nafo, I., Lipperverband, Germany

Pahl O., Glasgow Caledonian University, UK

Teedon P., Glasgow Caledonian University, UK

Chapter 2

Breure A.M., RIVM, Netherlands

van der Grinten E., RIVM, Netherlands

Lambooij M.S., RIVM, Netherlands

Lette M., RIVM, Netherlands

Russell C., Glasgow Caledonian University, UK (Box 2.1)

Chapter 3

Breure A.M., RIVM, Netherlands

Casellas M., EA 4330, Université de Limoges, FRANCE (Sludge)

Craft J., Glasgow Caledonian University, UK

Dagot C., EA 4330, Université de Limoges, FRANCE

Frew R.G., Glasgow Caledonian University, UK

Helwig K.P.M., Glasgow Caledonian University, UK

Hunter C., Glasgow Caledonian University, UK

Klepiszewski K., Luxembourg Institute of Science and Technology, Luxembourg

Lachassagne D., EA 4330, Université de Limoges, FRANCE (Sludge)

Levi Y., UMR 8079, Université Paris Sud, France (Ecotoxicity)

Lyko S., Emschergenossenschaft, Germany

MacLachlan J., Glasgow Caledonian University, UK

McNaughtan M.L., Glasgow Caledonian University, UK

Nafo, I., Lipperverband, Germany

Roberts J.B., Glasgow Caledonian University, UK

Wiest C., Institut des Sciences Appliqués CNRS Lyon, FRANCE (Analysis)

Perrodin Y., UMR, ENTPE, Lyon, France (Ecotoxicity)

Ploy. M.C., UMR Inserm 1092, Limoges, France (Antibioresistance)

Shu X., Glasgow Caledonian University, UK

Stalder T., EA 4330, Université de Limoges, France (Antibioresistance)

Chapter 4

Dagot C., EA 4330, Université de Limoges, FRANCE

Helwig KPM., Glasgow Caledonian University, UK

Mettoux-Petchimoutou A. P. , International Office for Water, Limoges, FRANCE

Nafo, I., Lipperverband, Germany

Shukla A., Glasgow Caledonian University, UK

Stuhr, K., Lipperverband, Germany

Teedon P., Glasgow Caledonian University, UK

Chapter 5

Lyko S., Emschergenossenschaft, Germany

Klepiszewski K., Luxembourg Institute of Science and Technology, Luxembourg

Venditti S., Luxembourg Institute of Science and Technology, Luxembourg

Chapter 6

Alrhmoun M., EA 4330, Université de Limoges, FRANCE

Dagot C., EA 4330, Université de Limoges, FRANCE

Gonzales Ospina A., Suez, FRANCE

Jiang JQ., Glasgow Caledonian University, UK

Klepiszewski K., Luxembourg Institute of Science and Technology, Luxembourg

Lyko S., Emschergenossenschaft, Germany

Venditti S., Luxembourg Institute of Science and Technology, Luxembourg

Chapter 7

Chan W., Glasgow Caledonian University, UK

Charissis V., Glasgow Caledonian University, UK

Khan S., Glasgow Caledonian University, UK

Nafo, I., Lipperverband, Germany

Pahl O., Glasgow Caledonian University, UK

Ramzan R., Glasgow Caledonian University, UK

Chapter 8 and 9

Dagot C., EA 4330, Université de Limoges, FRANCE

van der Grinten E., RIVM, Netherlands

Helwig K.P.M., Glasgow Caledonian University, UK

Klepiszewski K., Luxembourg Institute of Science and Technology, Luxembourg

Lambooij, M.S., RIVM, NL (Box 9.1)

Lyko S., Emschergenossenschaft, Germany

Nafo, I., Lipperverband, Germany

Pahl O., Glasgow Caledonian University, UK

Teedon P., Glasgow Caledonian University, UK (Box 9.1)

Editor

Pahl O., Glasgow Caledonian University, UK

Appendix 1 - Materials and Methods for Sampling and Analysis

Partner	Sampling Location(s)	Sampling dates	Composition (e.g. 24h composite)	Sampling regime	Interval between subsamples (if applicable)	Notes (e.g. wet weather / dry weather / summer/ winter)	Analytical method
Luxembourg	WWTP Schifflange (influent and effluent)	28 April 2014 – 8 June 2014	21 x 24-hr composites and 3x 7d composite	Flow proportional	200m^3	Period chosen to be entirely outside holidays to ensure normal operating conditions. Period includes separation campaign (12th May to 25th May 2015)	After filtration and enrichment by solid phase extraction (SPE), SPE extracts were analysed by LC-MS/MS (Agilent 1200SL on a Agilent Zorbax Eclipse Plus C18) with a gradient of two phases: phase mobile A (0.1% of formic acid in water) and phase mobile B (0.1% formic acid in methanol or acetonitrile depending on analytes : methanol used for naproxen, amoxicillin, carbamazepine, diclofenac and acetonitrile used for ciprofloxacin, clarithromycin, erythromycin, and sulfamethoxazole). Samples were detected using a mass spectrometer (AB Sciex Qtrap 4500 triple quadrupole) with electrospray ionization (ESI) in positive mode.
	WWTP CHEM influent and effluent	28 April 2014 – 8 June 2014	21 x 24-hr composites and 3 x 7d composite	Flow proportional	Continuous		
Germany	WWTP Dülmen (influent and effluent		24-hr composite	Time proportional			Process, standard and sludge parameters like TSS, COD, BOD, N and P were analyzed according to DIN. micro-pollutants were analyzed by different HPLC-MS and GC-MS methods. All samples were analyzed by the approved joint laboratory of the waterboards Emschergenossenschaft, Lippverband and Ruhrverband. By an extended, multiple-stage quality assurance including blanks, (75% marked) internal standards and interlaboratory tests reliable data could be ensured. All samples were direct injected after pre-filtration and centrifugation.
	Tiberbach (upstream and downstream from WWTP)						
	WWTP Marienhospital	2 September 2009 – 25 February 2015	24 composite	Flow Proportional			
France	Hospital effluent and WWTP Bellecombe effluent		24hr Composite samples	Flow Proportionate		Period chosen to be entirely outside holidays and weekends to ensure normal operating conditions.	After filtration and enrichment by solid phase extraction (SPE), SPE extracts were analysed by LC-MS/MS (Agilent 1100/1200 on a Agilent Zorbax Eclipse C18) with a gradient of two phases: phase mobile A (0.01 % acetic acid in water) and phase mobile B (methanol or acetonitrile depending on analytes : methanol used for paracetamol, , ketoprofen, diclofenac, atenolol, propranolol, econazole, carbamazepine, and the antibiotics ciprofloxacine, sulfamethoxazole, meropenem, aztreonam, vancomycine (positive mode) and acetonitrile/methanol 50/50 used for salicylic acid, ibuprofen, ethinylestradiol (negative mode)). Samples were detected using a mass spectrometer (AB Sciex Qtrap 3200 triple quadrupole) with electrospray ionization (ESI) in positive and negative mode.
	River Arve (upstream and downstream from WWTP)		24hr Composite samples	Flow Proportionate			

Partner	Sampling Location(s)	Sampling dates	Composition (e.g. 24h composite)	Sampling regime	Interval between subsamples (if applicable)	Notes (e.g. wet weather / dry weather / summer/ winter)	Analytical method
GCU	WWTP 1 influent and effluent	22-25 Sept 2014 and 20-24 Oct 2014	Daily 24hr composites. Influent only: also 2hr composites for 1 day	Influent: Flow proportionate Effluent: Time	Subsamples every 6 minutes; flow calculated for 2hr	Period chosen to capture a 'dry week' (Sept) and a 'wet week'	Samples were analysed using LC-MS/MS (Thermo Fisher Scientific Q Exactive Quadrupole Orbitrap mass spectrometer) in negative ion mode for diclofenac, ibuprofen, naproxen, simvastatin and triclosan, positive ion mode for all other pharmaceuticals. Deuterated internal standards were used where available.
				proportionate	intervals.	(Oct).	
	Breich Water upstream and downstream	22-25 Sept 2014 and 20-24 Oct 2014	Daily grab samples	l5 subsamples per grab sample	n/a		
	WWTP 2 influent and effluent	3-6 Nov 2014 and 9-12 March 2015	Daily 24hr composites. Influent and effluent: also 2hr composites for 1 day (not yet complete)	Influent: Flow proportionate Effluent: Time proportionate	Subsamples every 6 minutes; flow calculated for 2hr intervals.	Period chosen to capture a 'dry week' (Nov) and a 'wet week' (March).	
	How Burn upstream and downstream	3-6 Nov 2014 and 9-12 March 2015	Daily grab samples	5 subsamples per grab sample	n/a		
	River Almond catchment (7 locations)	30 June 2014– 3 July 2014	Daily grab samples	5 subsamples per grab sample	n/a		

Appendix 2 - Material and Methods for Advanced Treatment Trials

Experimental set-up in Germany (PP1)

The HWWTP consists of a combination of a membrane bioreactor (MBR) as a primary treatment step followed by advanced treatment with ozone and powdered activated carbon including a sand filtration step (PAC). Both the ozone and the PAC treatment steps are designed for the total effluent volume of the plant. All treatment steps were operated at default settings. An efficient mass transfer for ozone (ozone doses of 5 mg/L) is reached by five sequentially connected bubble columns equipped with inorganic diffusers. PAC is added via static mixer. Due to space or footprint restrictions a PAC sedimentation tank was not feasible. Thus, the PAC recycling in such a tank for a high PAC retention time could not be implemented. The high PAC dose of 20 mg/L should compensate that effect.

Experimental set-up in Luxembourg (PP3)

Five pilot-scale granular activated carbon columns were set up in order to investigate the removal of target pharmaceuticals present in the hospital MBR effluent. The columns have similar design with an internal diameter of 4 cm and a bed depth of around 50 cm of Norit GAC 830. The five columns are operated in up flow mode and fed in parallel with the same effluent but at different flow rates resulting in different Empty Bed Contact Times (EBCT), Hourly Space Velocity (HSV) and Hydraulic Loading Rate (HLR) as operational parameters.

The recommended HSV range is 0.1-3 nr/h depending on the degree of purification required, the type and concentration of impurity, the nature of the fluid and the pressure drop. For the removal of tracer of organic matter in fluid as wastewater, a HSV range of 2-3 nr/h can have good results (Norit, Technical Bulletin, TB 72B/02-03, V. 05-07).

For the reason mentioned above, Column 4 and 5 are columns of control. In the others, a higher influent flow is used to force an earlier saturation of the carbon. Columns conditions are summarized in table 1.

GAC Operation conditions	Column 1	Column 2	Column 3	Column 4	Column 5
Bed dept (cm)	51	54	55	55	55
D (cm)	4	4	4	4	4
Flow (l/h)	10	5.6	5	2.5	1.25
EBCT (min)	3.8	7.2	7.2	16.6	33.2
HSV (nr/h)	15.6	8.3	8.3	3.6	1.8
HLR (m/h)	7.958	4.476	3.979	1.989	0.995

Table 1: Operational conditions of the pilot scale study

For a correct operation of the columns it is necessary to monitor the MBR permeate quality to control the biofilm growth. The latter was performed by a routine flow test to observe any possible increase on pressure drop across the activated carbon bed and thus to prevent clogging. As result, a backwash procedure was executed concurrent with MBR permeate in order to remove excess biomass accumulated on the media. The effective backwash depends on the frequency and the volume of backwash cycle. As tertiary treatment backwashing was usually carried out every 3-4 weeks and more frequent in case of MBR malfunctioning (i.e. high transmembrane pressure).

In doing so, the GAC media is fluidized and expanded such that it releases bound organic/inorganic substances into the backwash water. Although a fraction of the bacterial biomass fixed on GAC may also be eliminated, the biofilm is generally resistant during this process.

Experimental set-up in France (PP6)

Classical Activated Sludge (CAS)

The CAS (figure 1) had a total volume of 14 L and was continuously fed with wastewater collected at the hospital. Influent flow rate was 21.6 L.d-1 (hydraulic residence time 15.3 h-1). Air flow rate was adjusted daily to maintain a dissolved oxygen concentration between 2 and 4 mg.L-1 in the reactors by repeated aerobic/anoxic cycles (2h/2h) in order to ensure nitrification and denitrification. Sludge recirculation (4) from the clarifier (3) was maintained at 100% feed flow rate. Solids residence time (i.e. sludge age) was maintained at 15 days throughout the experiments

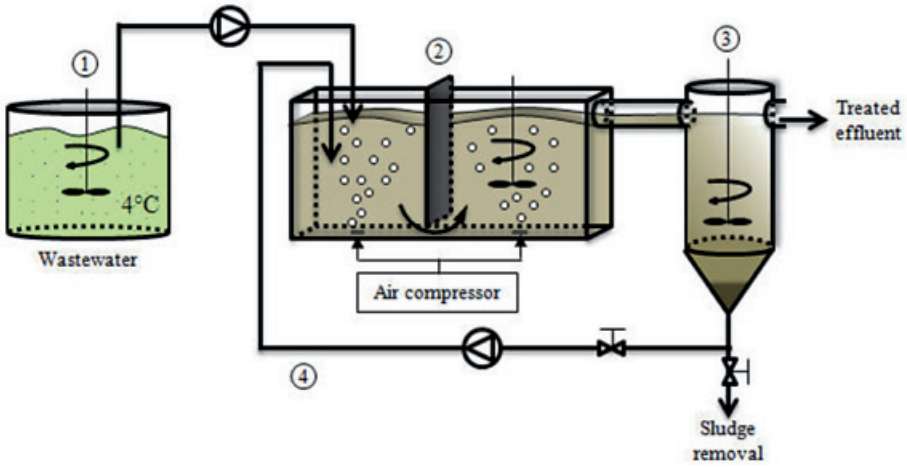


Figure 1: Classical Activated Sludge system

Membrane Bioreactor (MBR)

The MBR (figure 2) comprised a 30 L bioreactor and U-shaped hollow fibre membrane module was immersed in an aerated basin. Hollow fibres were made of polyethylene with a pore size of 0.05 µm (Mitsubishi Rayon Co., Ltd., Japan). Aeration (between 2 and 4.5mgO2/L) was done through diffusers at the bottom of the reactor to provide oxygen for biomass growth as well as shear to reduce cake formation at membrane surface. The membrane permeate was continuously removed by a peristaltic pump under a constant flux (1.8 L/h) and the trans-membrane pressure (TMP) was monitored to indicate the extent of membrane fouling. The operation was stopped when the TMP reached 26 kPa. The hydraulic retention time (HRT) ranged from 15 to 24 h and the sludge retention time (SRT) was around 15 days.

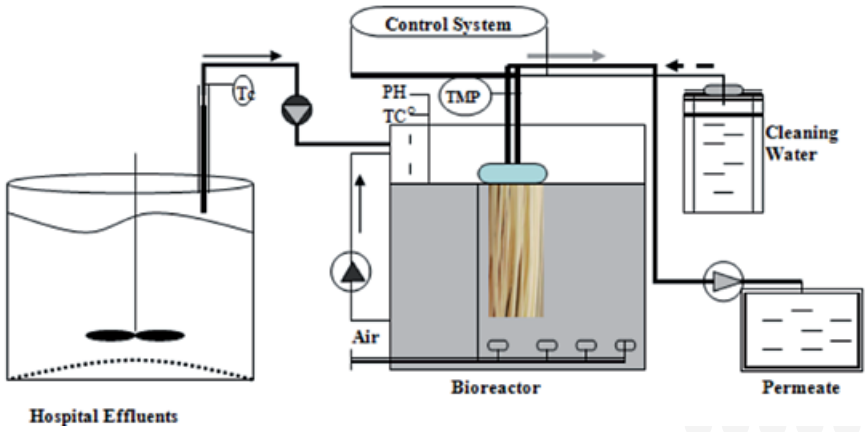


Figure 2: Membrane Bioreactor MBR

Parameter	CAS	MBR
HRT (h)	660	12,2
SRT (Days)	15	15 - 20
Flow (m3/h)	0,0009	0,0018
Temperature (°C)	17 - 20	16 - 19
pH	7,0 – 8,0	7,0 – 8,0
Disoolved oxygen (mg/L)	2,0 – 4,5	2,0 – 4,5
Volume aerobic tank (L)	14	30

Table 2: Key operational parameters of CAS and MBR systems investigated

Moving Bed Biofilm Reactor (MBBR)

The CAS and the MBR could be transformed in Moving Bed Biofilm Reactor by adding biofilm carriers on which a biofilm can grow. The properties of the carriers are reported in the table 3

The proportion of carriers added was about 40 to 50% of the total reactor volume.

Provider	Specific area (m2/m3)	Diameter (mm)	Length (mm)	Density	Material	Weight (kg/m2)
Stohr	660	12,2	12	0,95 – 0,98	PEHD	150

Table 3: Properties of carriers

Ultrafiltration system (AS-UF)

The reactor consisted of a bioreactor with a working volume of 400 L and a membrane module in Polypropylene, equipped with hollow fibers for a surface area of 1m and pore size of 0.2µm, and positioned in an external circulation loop (figure 3) (ALTING, MICRODYN, France). A Ruston turbine (80-120 rpm) was installed to keep the bioreactor completely mixed.

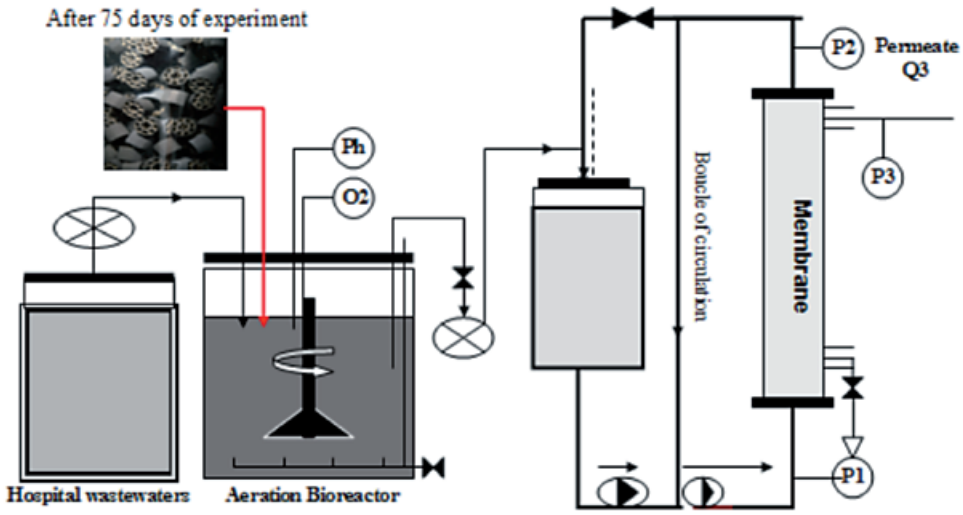


Figure 3: Ultrafiltration system

Operating characteristics were: influent average flow 100 L/day, permeate flow about 50 L/h, hydraulic retention time (HRT) 22 h, sludge retention time (SRT) around 20 days. Dissolved oxygen levels were maintained between 1 and 4.5 mg O2/L. The operation cycle was controlled automatically to 1h and 40 min. Pressures were measured at the inlet (P1), outlet (P2), and permeate side of the membrane (P3) in order to determine the transmembrane pressure (TMP).

Moving Bed Biofilm Reactor coupled ultrafiltration (BBR-UF)

The AS-UF could be transformed in a Moving Bed Biofilm Reactor by the same procedures than above, adding, in the biologic bassin, 50% (by volume) of carrier (figure 3). The aeration is sufficient to ensure a upward and downward movement for the biofilm carriers.

Moving Bed Biofilm Reactor coupled ultrafiltration and granular activated carbon

Two activated columns have been positioned at the output of the ultrafiltration to allow adsorption of the compounds which have not been oxidized or retained during the preceding operations (figure 4).

The GAC adsorbent (GAC-1240) was supplied by ''Norit Activated Carbon". Prior to the experiment the GAC was washed with distilled water to remove fine particles and then dried at 105°C for 24h. Two columns of borosilicate glass with internal diameter of 5 cm and active length of 75cm were used. The first column was filled with activated carbon in concentration 250gr of GAC/L and the second in concentration 375gr of GAC/L. GAC was devised to three equal parts before drying: at the top, it was washed by HCL (1N) in concentration 30% for 2h, in the middle by not wash and in the third by NaOH (1N).

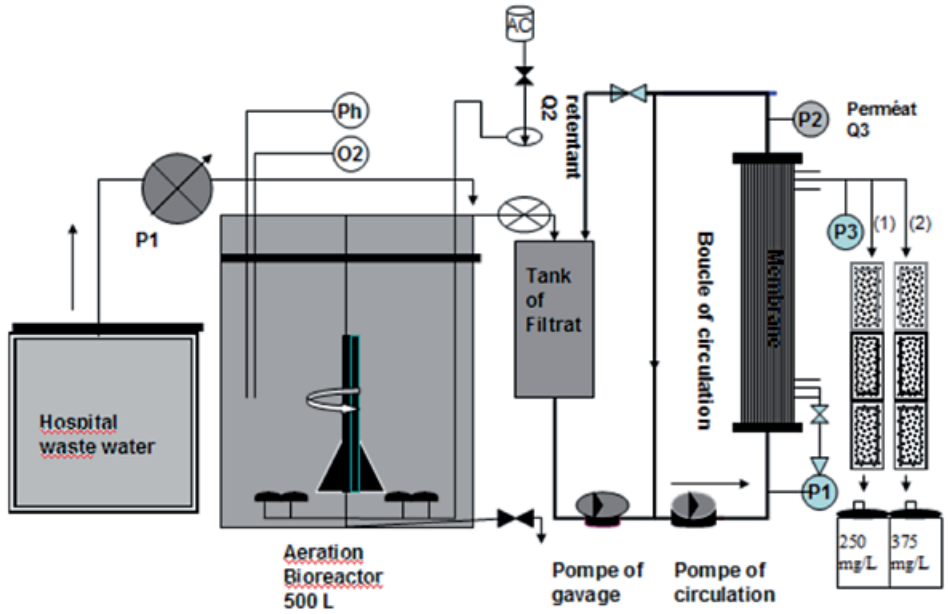


Figure 4: Ultrafiltration system coupled CAG

Ozone treatment of a mixed effluent, hospital and urban

A biological pilot treatment associated with an ozonation was tested on the experimental site of SIPIBEL (field observatory on hospital's effluents and urban wastewater treatment plants at Bellecombe WWTP – France, supported by Rhone-Mediterranean Corsica water agency, The Rhône Alpes Region and others partners) for the treatment of the hospital effluent of the CHAL (Hospital center Alpes Leman) (cf. chap ATBR – site presentation). This part, partially

associated with the noPills project, was also financially supported by the French Ministry of Economy, Industry and Digital within the framework of the Project TRIUMPH (TReatIng Urban Micropollutants and Pharmaceuticals in wastewaters) labelled and managed by the European Eureka Cluster ACQUEAU and the support of the French Agency for Environment and Energy Management (ADEME).

Two types of biological treatment were compared Activated sludge (AS) and Moving Bed Biological Reactor (MBBR) and the tertiary ozonation was realized in a contact column by applying various rates of treatment (4.5 mg/L, 13mg/L and 23 mg/L of transferred ozone) with optimized ozone transfer efficiency.

The pharmaceutical concentrations were followed in the biological waste sampled from the activated sludge with and without ozonation. Ozonation has used as pre-treatment of sludge before stabilizations treatments. The concentration of dry material was around 4 g/L and the dose of transferred ozone, according to the applied protocol, around 8g/L (that is 2mgO3/gMLSS).

Figure 5: Picture of the biological part of the Pilot

Experimental set-up in Scotland/ Germany (PP5)

The treatment procedures and analysis of collected samples after ferrate treatment at Emscher Technical WWTP of Germany can be seen in figure 6.

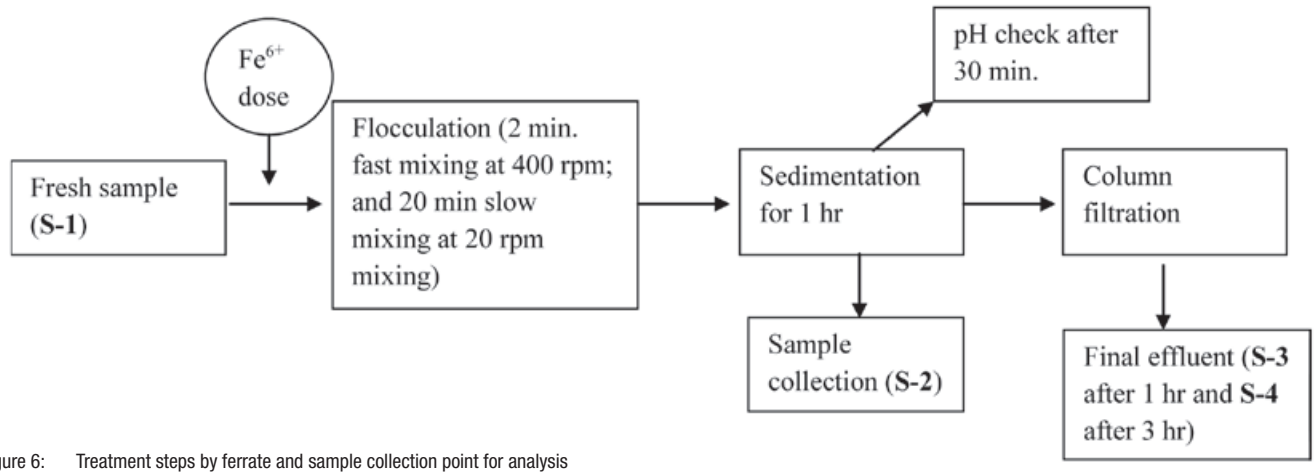


Figure 6: Treatment steps by ferrate and sample collection point for analysis

At the GCU laboratory, experiments were conducted using a standard jar test procedure; after dosing the required ferrate into effluent samples, a fast mixing was performed for 2 minutes at 250 rpm followed by 20 minute slow mixing at 25 rpm. After mixing, the suspension was kept for sedimentation for 1 hour and pH was measured after first 30 minute of sedimentation. Finally, the supernatant was collected followed by filtration through 0.45 µm and pH adjustment before analysing routine water quality parameters.

The concentrations of various water quality parameters were determined by HACH DR2800/DR3900 spectrophotometer using respective reagents from HACH LANGE, UK. Also, samples were prepared via filtration through 0.45µm, and stored for the analysis of pharmaceutical pollutants, which were measured either by the staff of Essen Water Laboratory when studies were carried out at Emscher Technical WWTP of Germany, or, by the staff at GCU when the experiments were conducted at GCU laboratories. The toxicity of the selected treated wastewater samples was preliminarily assessed by the Luminometer (BioFix Lumi-10) at the Water/Environmental Engineering Laboratory according to a Standard Method (British Standard BS EN ISO 11348-3) and then sent to the Life Sci. School's laboratory for them to carry out a further assessment by a zebra fish procedure (Dr Shu is leading his team for the assessment).

Acknowledgement

The noPILLS project has on the one hand benefitted from the previous PILLS project and supporters and outcomes from activities carried out and funded here. On the other hand noPILLS had a wide range of supporters and helping hands that enabled us to carry out our work in noPILLS for 3 years and to summarize in this report the main findings. We are grateful to have so many people that work together with us with the aim to make Europe a better place to live.

We would like to address special thanks from the **Emschergenossenschaft** as the Lead Partner to the helpful colleagues from the Interreg IV B Joint Technical Secretariat in Lille, namely Isabelle Lecroart, Olivier Rohas, Johanna März and internally the supporters Dr. Jochen Stemplewski and Dr. Emanuel Grün from the management board, Anke Althoff, Klaus Baumers, Frank Mertel, Till Möller, Ekkehard Pfeiffer, Michael Walkstein, Ingo Werner, Daniel Wischniewski.

Locally, we would like to express special thanks to the supporters at the Marienhospital project (in alphabetical order): Can Aksüt, Katja Albrecht, Cinzia Angenendt, Dirk Bausze, Carsten Bräuer, Christoph Breidenbach, Lars Günther, Timo Held, Christian Högel, Georg Jaensch, Peter Jagemann, Harald Jakobs, Dr. Uwe Keske, Julia Klinker, Dr. Ruben-Laurids Lange, Tommi Lindner, Dr. Sven Lyko, Willi Markwart, Cornelia Mohoric, Claudia Müller, Dr. Linh-Con Phan, Frank Pöller, Stefanie Roelecke, Dr. Joanna Will.

The **Dutch National Institute for Public Health and the Environment (RIVM)** would like to express special thanks to the supporting colleagues (in alphabetical order) Prof. Dr. Anton M Breure, Dr. Esther van der Grinten, Dr. Mattijs Lambooij, Drs. Manon Lette. The RIVM research was carried out in the framework of RIVM Strategic Programme (SPR), in which expertise and innovative projects prepare RIVM to respond to future issues in health and sustainability.

The **Luxembourg Institute of Science and Technology** would like to express special thanks to the colleagues (in alphabetical order) Dr.-Ing. Kai Klepiszewski and Dr. Silvia Venditti and to the supporters of the Centre Hospitalier Emile Mayrisch (CHEM): Alain Arend, Guy Bochen Eleonore Jung-Nimal, Christoph Schutz. Thanks as well to the supporters from SIVEC in Schifflingen: Gerry Bissen, Gianni Di Pentima, Jean-Marie Laurang. Moreover, special thanks go to the Swiss Eawag colleague Christa McArdell for the advice in the hospital campaign.

Special thanks in the **Lippeverband** project we want to express to the colleagues (in alphabetical order) John Assenmacher, Sabine Ladwig, Dr. Issa Nafo, Michael Steinbach, Kerstin Stuhr, Silke Wilts, Helmut Wissing, Peter zur Mühlen.

Furthermore special thanks to many supporters of the noPILLS project within the partner organizations, at consultants, and especially to the city of Dülmen. Even though many involved people are named below we had far more supporters and helpful hands in noPILLS:

Clemens Breulmann, Hubert Deipenbrock, Dr. Wolfgang Eichler, Patrik Gremme, Dr. Hubertus Hovestadt, Reinhild Kluthe, Clemens A. Leushacke, Jutta Reher, Johannes Röken, Barbara Schmitt, Franz-Josef Steverding, Lisa Stremlau, Bernhard Wielens, Christian Wohlgemuth.

The awareness campaigns in the city of Dülmen were designed with the support of external experts of RISP GmbH (Duisburg), ISOE (Frankfurt), INUC (Lüneburg), kib (Berlin), Signum GmbH (Mannheim). The local project in Dülmen was co-funded by the ministry of environment of the state of North Rhine-Westphalia.

The cooperation partners in the school projects were Marienschule, Privatschule Schloss Buldern, Clemens-Brentano-Gymnasium, Kardinal-von-Galen-Schule, Richard-von-Weizsäcker-Berufskolleg, Volkshochschule Dülmen and moreover Nabu Jugend Dülmen.

Glasgow Caledonian University would like to thank collaborators, members of the public, students and staff for their input into the project. In particular, thanks are due to Rob Cleat, John Cowan, George Ellen, Davie Kelly, Jim Matheson, John McGowan, Roi Otero, Robert Piercy, Chris Purves, Craig Stewart and Adam Zyndul of Scottish Water; Mark Heggie and Phil

Leeks of the Scottish Environment Protection Agency; Billy Malcolm and Kevin Milne of NHSScotland; Graeme Hedger, Eirwen Hopwood and Kirsty Morrison of West Lothian Council.

We wish to express our thanks to the fieldwork and support team at GCU and the University of the Highlands and Islands: Adeolu Aderemi, Graham Aikman, S.M. Ashekuzzaman, Mobolaji Ayoade, John Boyle, Steven Brown, Amaury Carlier, Magnus Davidson, Rohan Dhananjay Deogaonkar, Mathieu Farin, Richard Frew, Rachael Frost, Clementine Hill-O'Connor, Neil James, Simeon Journe, Kiana Kargar, Jill Noble, Kirsty MacFarlane, Eghiator Peter Osamudiamen, Zaniel Procopio, Kaitlin Ramsay.

Special consideration is due to the attendendees of our Game Jams in 2014 and 2015 (especially Kenny Campbell, David Carr, Farhad Chamo, Mihael Galchev, Kieran Gallagher, Andrew Graham, Connor Johnston, Antony Lingard, Réka Lux, Mark Tempini and the boys and girls of Elmvale Primary School P6 2015 class), the boys and girls of Netherlee Primary P7 and Thornhill Primary P1-3 class of 2014, and in addition we would like to thank those who attended a pilot engagement workshop within GCU.

We would like to acknowledge members of the communities who agreed to take part in interviews and workshops – we do not identify them (individuals or communities) specifically as their anonymity was guaranteed in line with ethical considerations.

Last not least, we would like to express thanks to all technical and academic staff at GCU who also contributed to the project, in particular: Robert Adamson, Geraint Bevan, Colin Dalglish, John Graham, Susan Grant, Iain Hamilton, Brian Leiper, Derek Leitch, Robert Liddell, Andrew Mason, David Moffat, Jessica Russell, Angela Shapiro, Stacey Taylor, Graham Wylie.

The **Université de Limoges** wants to express special thanks to the supporters from GRESE and the university (in alphabetical order) Dr. Moussab Alrhmoun, Prof. Christophe Dagot, Lourdes Ferreira, Dr. Delphine Lachassagne, Corinne Maftah, Prof. Casellas Magali, Dr Thibault Stalder. Thanks to the UMR INSERM 1092 colleagues Prof. Olivier Barraud, Mrs Margaux Gaschet and Prof. Marie Cécile Ploy. Thanks to the UMR CNRS 7285 Université de Poitiers supporters Prof. Jerôme Labanowski, Mrs Elodie Laurent. Thanks to the supporters from GRAIE – SIPIBEL in Lyon Elodie Brelot and Vivien Lecomte, from DEGREMONT SUEZ Dr Adriana Gonzales Ospina and from OIEAU Mrs Anne-Paule Mettoux-Petchimoutou.

The French evaluations were supported, in addition to the noPILLS project, by Rhone-Mediterranean Corsica water agency, The Rhône Alpes Region and others partners.

Last not least

The noPILLS partnership is grateful for the continued support and advice provided by the members of the project's Advisory Board. We would like to pay special thanks to Andreas Hartmann and Jutta Hellstern (Novartis, Switzerland), Christa McArdell (Eawag, Switzerland), Peter Robbins (Open University, UK), Thomas Steger-Hartmann (Bayer HealthCare, Germany) and Luc Zwank (Administration de la gestion de l'eau, Luxembourg).

…and finally:

a special big "Thank you!" to Kirsten Adamczak of EGLV, for her ability to stay calm in the face of financial reporting, looming deadlines and unruly researchers. Thanks for making us read all the lines ;-) and for organising our every step (literally) during meetings!

NO pills IN WATERS

Investing in Opportunities

This project has received European Regional Development Funding through INTERREG IV B.

INTERREG IVB

Impressum

EMSCHERGENOSSENSCHAFT

Kirsten Adamczak
Kronprinzenstrasse 24
45128 Essen, Germany

Phone: 0049 - 201 104 2679
E-mail: adamczak.kirsten@eglv.de

www.no-pills.eu

edition June 2015